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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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CIRCULATORY SYSTEM DEVICES PANEL

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May 7, 2014
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

PANEL MEMBERS:

JOHN W. HIRSHFELD, JR., M.D.	Temporary Panel Chair
RICHARD A. LANGE, M.D., M.B.A.	Voting Member
DAVID D. YUH, M.D.	Voting Member
KEITH B. ALLEN, M.D.	Temporary Non-Voting Member
RICHARD D. BRANSON, M.S., RRT	Temporary Non-Voting Member
RALPH BRINDIS, M.D., M.P.H.	Temporary Non-Voting Member
HUGH A. CASSIERE, M.D., FCCP	Temporary Non-Voting Member
JOAQUIN CIGARROA, M.D.	Temporary Non-Voting Member
RALPH B. D'AGOSTINO, SR., Ph.D.	Temporary Non-Voting Member
DAVID C. GOOD, M.D.	Temporary Non-Voting Member
RICHARD A. JONAS, M.D.	Temporary Non-Voting Member
DAVID E. KANDZARI, M.D.	Temporary Non-Voting Member
MICHAEL F. O'CONNOR, M.D.	Temporary Non-Voting Member
STEVEN D. NATHAN, M.D.	Temporary Non-Voting Member
KENTON ZEHR, M.D.	Temporary Non-Voting Member
NAVEEN THURAMALLA, M.S., CCRP	Industry Representative
DEBRA McCALL, B.S., MAM	Patient Representative
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M E E T I N G

(8:10 a.m.)

DR. HIRSHFELD: Good morning, everybody. It's 8:10, and I would like to call this meeting of the Circulatory System Devices Panel to order.

My name is John Hirshfeld, and I will serve as your Chair. I am an interventional cardiologist. I'm a Professor of Medicine at the University of Pennsylvania School of Medicine.

And I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I'd also like to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

And for today's agenda, our Panel will discuss and make recommendations regarding the classification of membrane lung for long-term pulmonary support systems, commonly referred to as extracorporeal membrane oxygenation. And our purpose is to either reconfirm the current status of Class III or to potentially reclassify to Class II.

And before we begin, I would like our distinguished Panel members and FDA staff seated at the table to introduce themselves. And please state your name and your area of expertise and your position and your affiliation. And we'll start with Mr. Thuramalla.

MR. THURAMALLA: Good morning, everybody. I am

Naveen Thuramalla. I'm the VP of Engineering and Clinical Studies at Transonic Systems. I'm serving as the Industry Representative on this Panel.

MS. MATTIVI: Good morning. Kris Mattivi. I'm the Consumer Representative to the Panel. I'm a physical therapist and a business analyst at WellPoint.

MS. McCALL: Debra McCall. I'm the Patient Representative. I'm a volunteer with StopAfib.org and the Healthy eHeart Study.

DR. O'CONNOR: I'm Michael O'Connor. I am an anesthesiologist and intensivist at the University of Chicago.

MR. BRANSON: Rich Branson. I'm a respiratory therapist, and I'm Professor of Surgery and Director of Clinical Research in the Department of Surgery.

DR. GOOD: Good morning. My name is David Good. I'm Professor and Chair of Neurology at Penn State College of Medicine, Hershey.

DR. D'AGOSTINO: Ralph D'Agostino, statistician from Boston University and the Framingham Study.

DR. ZEHR: Hi, Kenton Zehr. I'm an Associate Professor of Surgery at the Johns Hopkins Hospital, and I do adult cardiac surgery.

DR. BRINDIS: Ralph Brindis, Clinical Professor, UCSF Institute for Health Policy Sciences. I'm a interventional cardiologist by training and also the Senior Medical Officer of the National Cardiovascular Data Registry.

DR. ALLEN: My name is Keith Allen. I'm Director of Surgical

Research and a cardiothoracic as well as vascular surgeon at the St. Luke's Mid-America Heart Institute in Kansas City, Missouri.

DR. LANGE: Howdy. I'm Rick Lange. I'm Professor of Medicine at the University of Texas Health Science Center in San Antonio, where I'm the Vice Chairman of Medicine. And my training is in interventional cardiology.

MS. WATERHOUSE: Jamie Waterhouse. I'm the Designated Federal Officer for FDA.

DR. CIGARROA: Good morning. I'm Joaquin Cigarroa, Clinical Professor of Medicine at Oregon Health Science University. I'm an interventional cardiologist and the Clinical Chief of the Knight Cardiovascular Institute.

DR. CASSIERE: Good morning. Hugh Cassiere, Chief of Critical Care, Director of the Cardiothoracic Intensive Care Unit, North Shore University Hospital, Manhasset, New York, and my expertise is cardiothoracic critical care.

DR. YUH: Good morning. My name is David Yuh. I'm Professor and Chief of Cardiac Surgery at Yale University in New Haven, Connecticut.

DR. KANDZARI: Good morning. I'm David Kandzari. I'm an interventional cardiologist, and I practice critical care intensive medicine as well, and I'm the Chief Scientific Officer at the Piedmont Heart Institute in Atlanta.

DR. JONAS: Good morning. I'm Richard Jonas, Chief of Cardiac Surgery, Children's National Medical Center in Washington, D.C.

DR. NATHAN: Steve Nathan. I'm an adult pulmonologist and intensivist, and I'm the Medical Director of the Lung Transplant Program at Inova Fairfax Hospital, which is in Falls Church, Virginia.

DR. ZUCKERMAN: And Bram Zuckerman, Director, FDA, Division of Cardiovascular Devices. Thank you.

DR. HIRSHFELD: Well, thank you. And I'm delighted that we have such a distinguished panel with a broad range of expertise to deal with this question that we're going to deal with today.

I would just like to remind all of those of you who are carrying electronic things that beep, if you would please arrange for them to be silent for the duration of the meeting, that will be helpful.

Now, if you've also not already done so, please sign the attendance sheets that are on the tables by the doors. And Ms. Waterhouse, who is our Designated Federal Officer for the Circulatory System Devices Panel, she is going to make some introductory remarks.

MS. WATERHOUSE: Good morning. I will now read the Conflict of Interest Statement. The Food and Drug Administration is convening today's meeting of the Circulatory System Devices Panel of the Medical Device Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative,

all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S. Code Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S. Code Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflicts of interest.

Related to the discussion of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S. Code Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss and make recommendations regarding the classification of membrane lung for long-term pulmonary support systems, commonly referred to as ECMO, to either reconfirm to Class III or reclassify to Class II. The Panel will also comment on whether special controls are adequate to ensure the safety and effectiveness of this device in an adult patient population. ECMO is currently used for patients with acute reversible respiratory or cardiac failure unresponsive to optimal ventilation and/or pharmacologic management.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S. Code Section 208.

Naveen Thuramalla is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Transonic Systems.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

For the duration of the Circulatory System Devices Panel on May 7th, 2014, Ms. Debra McCall has been appointed as a temporary non-voting member. For the record, Ms. McCall serves as patient representative to the Cardiovascular and Renal Drugs Advisory Committee in the Center for Drug Evaluation and Research. This individual is a special Government employee who has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting.

The appointment was authorized by Jill Hartzler Warner, Acting Associate Commissioner for Special Medical Programs, on April 25th, 2014.

Before I return the meeting back over to Dr. Hirshfeld, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting.

Information on purchasing videos of today's meeting can be found at the FDA meeting registration desk.

The Press Contact for today's meeting is Susan Laine.

I would like to remind everybody that members of the public and press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA

officials until after the Panel meeting has concluded.

If are presenting in the Open Public Hearing today and have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and other electronic devices at this time.

Thank you.

DR. HIRSHFELD: Thank you, Ms. Waterhouse.

We will now begin with a discussion of the reclassification process and criteria. So we will hear from Geeta Pamidimukkala, who will orient us to this.

And I would like to remind all the public observers that while this meeting is open for public observation, public attendees may not participate except at the request of the Panel Chair.

MS. PAMIDIMUKKALA: Good morning. My name is Geeta Pamidimukkala. I'm on the 510(k) staff at the FDA, and we manage the 510(k) program.

Okay. Today we're meeting to get input from you, the Panel and the audience speakers, to provide your recommendations for the classification of a preamendments device type. And this will help FDA to

determine whether or not to call for a PMA for this device type or to reclassify it into Class II or Class I.

A preamendments device is a device defined by, determined by when it entered interstate commerce. So devices that were introduced into interstate commerce prior to May 28th, 1976, which is the enactment date of the Medical Device Amendments Act, are considered preamendments devices.

There are three device classes for all FDA-regulated medical devices, and they are defined by the level of controls necessary to have a reasonable assurance of safety and effectiveness. Class I is the lowest class of devices, and these are defined by the use of general controls solely for the assurance of safety and effectiveness. Class II devices utilize general and special controls to assure safety and effectiveness. And Class III devices require a premarket approval. All devices are placed into the lowest class whose level of control provides a reasonable assurance of safety and effectiveness.

General controls include a prohibition against adulterated or misbranded devices, adherence to good manufacturing practices, registration of the manufacturing facility, the device should be listed with the FDA, and maintenance of good recordkeeping.

Some examples of special controls include conformance to performance standards, postmarket surveillance, patient registries, or the

development and dissemination of guidance documents or guidelines.

Class I devices are devices for which general controls alone are sufficient to provide reasonable assurance of safety and effectiveness. And these devices typically don't require any premarket review by the FDA prior to being marketed. Another way to think about Class I devices are devices that cannot be considered Class III because they're not life-sustaining or life-supporting or of substantial importance in preventing impairment of public health, and because they don't present a potential unreasonable risk of illness or injury. They also cannot be considered Class II devices because insufficient information exists to establish special controls to provide a reasonable assurance of safety and effectiveness.

Some examples of Class I devices are general cardiovascular surgical instruments, adhesive bandages, manual stethoscopes, and crutches.

Class II devices cannot be classified into Class I because general controls alone are insufficient to provide reasonable assurance of safety and effectiveness, and we do have sufficient information to establish special controls that would provide such assurance. Class II devices typically require a 510(k) notification prior to being marketed.

Some examples of Class II devices include blood pressure cuffs, percutaneous catheters, the electronic stethoscope, vascular graft prosthesis, ECG, hemodialysis system, and syringes.

An example of how special controls are used: For the PTCA

catheters, they were reclassified from Class III to Class II using special controls. FDA identified the special controls that were necessary to establish a reasonable level of safety and effectiveness. These special controls included biocompatibility testing, bench testing, animal testing, sterility and shelf life requirements, and labeling requirements, such as warnings, precautions, adverse events. All of these were identified and issued in a guidance document for these devices. These special controls, in combination with the general controls, do provide a reasonable assurance of safety and effectiveness. And companies must provide evidence in their 510(k) submission of how these special controls were addressed.

Class III devices are devices for which insufficient information exists to determine that general controls and special controls are sufficient to provide reasonable assurance of safety and effectiveness, and these devices are life-sustaining or life-supporting, they are also of substantial importance in preventing impairment of human health, or they present a potential unreasonable risk of illness or injury. Class III devices typically require a PMA prior to being marketed.

Some examples of Class III devices include endovascular grafts, coronary and peripheral stents, percutaneous heart valves, LVADs, cardiac occluders, and implantable pacemakers.

There are some 510(k) Class III devices for which 510(k)s are still reviewed prior to coming to market. These are devices that are

preamendments, and FDA has issued a proposed rule to classify them as Class III. However, a final rule was never issued, or the final rule was issued but a final date was never established that began requiring companies to submit a PMA. So these devices are classified as Class III but they are allowed to proceed to market via the 510(k) process until FDA issues a final date requiring a PMA or makes a final rule to reclassify it as Class III.

The reclassification process for a preamendments device can occur in a proceeding that parallels the initial classification of the proceeding. It can be based on new information for the respective, either on FDA's own initiative or upon the petition of an interested person. The Agency can classify or reclassify intended uses which have actually been reviewed by the Agency.

The process for which preamendments devices are classified by the FDA is after the FDA has reviewed the recommendations from the Panel, we will issue a proposed order announcing our proposed classification and seek public comment. Then we'll hold this Panel meeting to classify or reclassify the device type. And we'll consider all of the comments that are available, including your recommendations from the Panel. And then we'll issue a final order finalizing the classification of the device type.

This is a useful flowchart in determining what is the classification for a device. And the first question to ask yourself is whether general controls alone are sufficient to assure a reasonable level of safety

and effectiveness. If yes, then we would determine this device to be Class I. If no, the next question to ask is whether or not sufficient information is available to establish special controls to assure a reasonable level of safety and effectiveness. If yes, then this device is considered Class II. If no, then next question is whether or not the device is life-supporting or life-sustaining or is of substantial importance to human health. If it's yes, the device is Class III. If no, then the next question to ask is whether or not the device raises a potential unreasonable risk. If not, then this device can be classified as Class I. If yes, it is classified as Class III.

From the Panel, we need input on whether or not to classify this device into Class III, Class II, or Class I. Your input should include an identification of all risks to health, if any, that are presented by the device. You should consider whether or not the device is life-sustaining or life-supporting or of substantial importance in preventing impairment to human health, or if it presents an unreasonable risk of illness or injury. And you should also identify whether or not sufficient information exists to develop special controls, and if yes, you should identify what those special controls are.

After this meeting, FDA will consider all of the recommendations made here. The proposed order has actually already gone out for this device, and so following this Panel, FDA will consider your recommendations and make a final order identifying the appropriate class. If

it's Class I or Class II, the devices can continue to be marketed. If it's Class III, FDA will issue a separate call for PMAs, and it will require the premarket approval for all of these device types.

And that's it.

DR. HIRSHFELD: Okay. Thank you very much.

Do any of the Panel members have any question for Ms. Pamidimukkala?

(No response.)

DR. HIRSHFELD: I see no questions, so Geeta, thank you very much. You're off the hook.

Okay. We will now move to the FDA presentation, which will be given by Catherine Wentz.

I'm sorry. There is a question for Geeta.

DR. LANGE: Geeta, this is Rick Lange. I just wanted a clarification, because it wasn't mentioned in your presentation, is that a device can have a Class II or a Class III recommendation, the same device, for different indications; is that correct? Would you clarify that?

MS. PAMIDIMUKKALA: That's right. A device type can be split into two different categories. It could be Class II and simultaneously Class III, and that would be based on a parsing of the intended uses for those devices.

DR. LANGE: Okay. And then the follow-up: Is it the purpose of the FDA to regulate use of these or availability of these devices to physicians?

MS. PAMIDIMUKKALA: So the FDA does not regulate the practice of medicine, but once we determine how a device is intended to be used and the appropriate classification, that will determine the route to market for that device.

DR. LANGE: Okay. So this has to do with -- more with marketing than availability of the device?

MS. PAMIDIMUKKALA: So the -- I guess --

DR. ZUCKERMAN: Geeta, so I think the question that Dr. Lange is referring to is this helps us define indications for use and appropriate regulatory pathways for legal device clearance or approval. But we don't regulate the practice of medicine, as you're indicating, Geeta, and consequently, there's always the potential for off-label device use in circumstances where physicians believe that the circumstances and other literature data support that use.

MS. PAMIDIMUKKALA: Right. FDA does not regulate the applications or the availability of these devices in the market, but it does regulate the path to market.

DR. LANGE: Thank you very much.

DR. HIRSHFELD: Ms. Wentz, will you proceed?

MS. WENTZ: Thank you.

Good morning. My name is Catherine Wentz, and I will begin the presentation today regarding the classification and regulation of the

membrane lung for long-term pulmonary support. Specifically, today's discussions will focus on the use of ECMO therapy in the adult patient population.

The FDA speakers today will be myself, Dr. Avila-Tang, Dr. Laschinger, and Dr. Jison.

The outline for this part of the FDA presentation will include the specific objective of this Panel meeting and some important historical information, including a discussion regarding a membrane lung for long-term pulmonary support versus an extracorporeal membrane oxygenation, or ECMO, procedure; a description of an ECMO circuit; a discussion of the devices and indications cleared for ECMO; a brief regulatory history; the voluntary medical device reports, or MDRs; and finally, the identified risks to health when considering an ECMO circuit.

So what is the objective of this Panel meeting? In September 2013, FDA convened the Circulatory Devices Advisory Panel to discuss the regulation of the devices used in an ECMO circuit specifically in pediatric patients. Recommendations were made to reclassify the membrane lung for long-term pulmonary support regulation from Class III to Class II in pediatric populations for certain reversible respiratory and cardiorespiratory conditions. The Panel also requested that FDA review the available ECMO literature for adults and convened another Panel meeting to discuss the additional clinical application in order to inform a more comprehensive final

recommendation for the classification of the membrane lung for long-term pulmonary support. As such, today's Panel meeting will be focused on a discussion of the available information related to adult respiratory and cardiorespiratory indications for ECMO.

We will present the information researched and request Panel input on the level of evidence available for ECMO therapy when utilized in the adult patient population for respiratory and cardiorespiratory conditions. FDA will consider today's discussion on the adult patient population in conjunction with the previous recommendations made by the Panel during the September panel meeting regarding the pediatric patient population to inform a final recommendation regarding the classification for the membrane lung for long-term pulmonary support.

21 C.F.R. 868.5610, which is the regulation number for the membrane lung for long-term pulmonary support, currently identifies the oxygenator component only of an ECMO circuit. As discussed during the September 12th panel meeting, the oxygenator alone cannot perform ECMO therapy. As such, one of the items proposed in the January 8th, 2013 proposed order, as well as during the September panel meeting, both of which will be discussed shortly, was to broaden the regulation to include all of the circuit components and accessories needed for long-term extracorporeal support, as well as build in flexibility into the identification to provide an efficient approach to regulate the individual components of an

entire system that provides and/or participates in long-term extracorporeal support.

To go into a little more detail regarding the current definition for the membrane lung for long-term support regulation, that is, defining a single device versus an ECMO circuit, which is needed to provide the appropriate therapy, I would like to show you the following two slides. Based on the original and current identification for this regulation, the identification describes only an oxygenator that would be used for long-term gas exchange. That is, a membrane lung for long-term pulmonary support is a device used to provide a patient extracorporeal blood oxygenation for longer than 24 hours. ECMO therapy, however, can't be performed with an oxygenator alone and is provided via an extracorporeal circuit comprised of many devices, including but not limited to, the oxygenator, a pump, cannula, heat exchanger, tubing, et cetera.

ECMO is a medical therapy delivered to patients with respiratory failure, cardiorespiratory failure, and most recently, cardiac failure. Since we are considering the safety and effectiveness of ECMO therapy in these conditions, we will need to consider all of the devices that are utilized in an ECMO circuit and that contribute to the therapy.

Next, I would like to identify the devices and indications that have been cleared either under the membrane lung for long-term pulmonary support regulation or have been cleared for use with ECMO labeling. Besides

an oxygenator, FDA has also cleared tubing, heat exchangers, and catheters for use in ECMO circuits. Bear in mind that based on device size, design and/or supporting data, most of the devices originally cleared for ECMO have been intended for pediatrics, neonates and/or infants.

The cleared indications for use include the following. Tubing was cleared in 1977 for use with roller pumps, which were the only pumps used for ECMO at that time. An oxygenator was cleared in 1986 for long-term ECMO procedures with labeling indicating use up to 32 days. And the cleared indications for heat exchangers and catheters state that the devices are intended for use during ECMO procedures.

I will make the regulatory history discussion brief but will highlight the recent regulatory activity, including the January 8th, 2013 proposed order and the September 12th, 2013 panel meeting to provide you with the appropriate background to frame today's discussion.

Here is a snapshot of the regulatory history for the membrane lung for long-term pulmonary support. The Advisory Panel's recommendation that membrane lung devices for long-term pulmonary support be classified as a Class III device was published as a final rule on July 16th, 1982. However, no effective date had been established for the requirement for premarket approval for these devices, so they have been reviewed and cleared under the 510(k) regulation.

In 1995, a 515(i) classification order was published and resulted

in a citizen's petition being submitted in 1998, recommending reclassification of ECMO to Class II. A final rule was never issued after the 1995 order, so on April 9th, 2009, another 515(i) classification order was published, requesting information from interested parties and manufacturers regarding the safety and effectiveness of the membrane lung for long-term pulmonary support for a classification panel. The information received in response to the April 9th order was from the sole manufacturer of an oxygenator cleared for long-term use and consisted of a copy of the 1998 citizen's petition along with some minor updates and a new medical device report, or MDR, analysis.

As in 1998, the response was in favor of reclassification to Class II based on the history of use for the device, the proposed special controls to mitigate the risks to health associated with the device, and the 30-plus years of data from the Extracorporeal Life Support Organization registry, also known as the ELSO registry.

This brings us to the January 8th, 2013 proposed order. Based on the response to the April 9th, 2009 as well as the known regulatory and scientific history for the membrane lung for long-term pulmonary support, the FDA published the January 8th, 2013 proposed order recommending reclassification for the membrane lung for long-term pulmonary support from Class III (premarket approval) to Class II (special controls) for conditions where imminent death is threatened by cardiopulmonary failure in neonates and infants or where cardiopulmonary failure results in the inability to

separate from cardiopulmonary bypass following cardiac surgery. FDA further proposed to revise the title and identification of the regulation to reflect all device components used in an ECMO circuit, not just the oxygenator.

On September 12th, 2013, the Food and Drug Administration and the Circulatory System Device Advisory Committee convened to discuss the classification of the membrane lung for long-term pulmonary support in the pediatric patient population. The Panel discussion involved making recommendations regarding regulatory classification to either reconfirm Class III or reclassify to Class I or Class II. To this end, the Panel was asked to provide input on the risks to health, safety, and effectiveness of the use of ECMO in the pediatric patient population.

Following significant discussion, the Panel agreed with the reclassification proposal to Class II for certain reversible respiratory and cardiorespiratory conditions in the pediatric patient population with the special controls identified on this slide. Details regarding these special controls were provided in the Executive Summary and will be identified again in the questions to the Panel.

The Panel also recommended that FDA perform a review of the available literature regarding the use of ECMO in adults and reconvene a Panel meeting to discuss this data, which brings us here today to discuss the safety and effectiveness of the membrane lung for long-term pulmonary

support for the adult patient population.

As mentioned earlier, the September 12th panel meeting made the recommendation for reclassification from Class III to Class II for the pediatric population for certain respiratory and cardiorespiratory conditions where death is imminent. Today's discussion will focus on the information available regarding the use of ECMO in the adult patient population. Ultimately, the final order put forward by the FDA for the reclassification of the membrane lung for long-term pulmonary support will have considered comprehensive discussions from both the September panel meeting, which covered the pediatric population, as well as today's Panel meeting, which will cover the adult population.

The clinical evidence presented today will include MDR reports and recalls, a systematic literature review, and current clinical evidence and experience with ECMO in the adult patient population. I will cover the MDR reports and recalls. The systematic literature review and current clinical evidence and experience will be covered by the subsequent FDA presenters.

The FDA Executive Summary included a series of MDR reports, which attempted to tell the story of the difficulty in identifying adverse event reports related to ECMO procedures. In short, MDR reports are identified by device type. ECMO procedures require the use of an extracorporeal circuit, which could include many device types. So more often than not, it is difficult to determine which event may have been attributed to which device.

Additionally, since most of the devices utilized in an ECMO circuit are being used off-label, that is, most of the devices used for ECMO are actually cleared for short-term cardiopulmonary bypass procedures, it is difficult to determine whether the report was related to an ECMO procedure or a bypass procedure.

This table shown here provides the most comprehensive attempt in identifying the issues related to an extracorporeal circuit, as the search included 10 circuit devices as well as the search term "ECMO." And this search is identical to search number 2 provided in your Executive Summary.

The search yielded a total of 340 MDRs. Malfunctions were the most frequently reported type of event with 58 reported deaths over the 11 years. Some of the device problems identified in these MDR reports include the list shown here in the general order of prevalence with the replacement of a circuit device occurring in approximately 20 to 30% of these reports. Blood loss was the only specific commonly reported patient issue.

This table represents a list of device recalls for all ECMO circuit components. Since recalls typically reflect design controls or manufacturing issues that would apply regardless of the use of the device, these recalls do not necessarily reflect failures specific to ECMO use. It should be noted that recalls are classified into a numerical designation, I, II, or III, by the FDA to indicate the relative degree of health hazard presented by the product being

recalled, with Class I being the most severe. In total, there have been three Class I recalls over the past 11 years.

Lastly, I would like to go over the risks to health identified for ECMO as a therapy and inclusive of the entire ECMO circuit, not just the oxygenator. So before I go into the specific risks to health for ECMO, I'd like to cover the more general concept of a risk to health versus an adverse event. A risk to health is a direct risk associated with the use of the device type, for example, inadequate gas exchange for an oxygenator or hemodilution for the entire circuit. An adverse event would be a potential clinical consequence of the risk. For example, inadequate gas exchange could lead to death; hemodilution could lead to kidney failure.

So with the definition of a risk to health in mind, the risks to health identified for the membrane lung for long-term pulmonary support regulation are shown above. These risks to health were also presented in the January 8th, 2013 proposed order as well as the September panel meeting, where the pediatric population was discussed. FDA believes that the risks to health for the adult population are identical to those identified during the September panel meeting for the pediatric patient population.

The first seven risks identified on this slide include the risks identified by the original anesthesiology panel in 1979, which are the first four risks in italics, as well as those identified in the 1998 citizen's petition, which are the three highlighted in yellow. One should note that these first

seven risks were all based on the original regulation identifying an oxygenator only. The final four risks in bolded type were added to identify the risks to health associated with an ECMO procedure, which include considerations related to the therapy as well as all of the circuit components. Again, please note that these are the same risks to health that were presented during the September 12th, 2013 panel meeting where the pediatric patient population was discussed, and FDA believes that this list applies to the adult population as well.

Thank you. And at this time, I would like to present Dr. Avila-Tang, who will discuss the systematic literature review performed and the methods used.

DR. AVILA-TANG: Good morning. I'm Dr. Erica Avila-Tang, and I'll be presenting the results of a systematic literature review on the use of extracorporeal membrane oxygenation among adults that the Division of Epidemiology prepared.

The objective of this literature review is to provide safety and effectiveness information for the use of veno-arterial and veno-venous extracorporeal membrane oxygenation among adults.

This is the list of the indications for use for veno-arterial ECMO that were used for this literature review.

This slide presents the list of indications for use that were included for veno-venous ECMO.

Next, I will be presenting the methods we used in this literature review. A search of the scientific literature was conducted using PubMed on December 16, 2013. This search used ECMO as a major MeSH term, and additional MeSH terms were used for indications for use, age groups, humans, and English language. The text "Extracorporeal Life Support Organization" was also included to identify articles using data from each international registry. Articles published on June 1st, 2012 and thereafter were not indexed in PubMed at the time of the literature search. Therefore, an additional search was conducted without using MeSH terms from June 1st, 2012 and December 16, 2013.

Studies were excluded if they were case reports, small studies, nonsystematic reviews or nonclinical studies; if they did not present results for ECMO, indications for use, or adult patients; and if ECMO support was for less than 24 hours, ECMO was used with adjunct treatments, or if the studies were conducted before 2000.

This slide presents the article retrieval and selection process for this literature review. There were 700 articles identified through PubMed on December 16, 2013. After reviewing titles and abstracts, 490 were removed using the exclusion criteria, and therefore, 210 full-text articles were reviewed, with 28 included.

Out of the 28 articles identified, the study designs included one meta-analysis, one randomized clinical trial, two cohort and one case-control

studies, and 23 case series which included a number of registry-based studies. Two studies were based on data from the Extracorporeal Life Support Organization international registry. The other studies were conducted among patients in the United States and a number of countries in Europe and Asia. These studies were published between 2008 and 2013. Results will be presented by indication for use.

Here's a summary of the number of studies identified by indication for use, type of study design, and sample size. There were studies that presented data for more than one indication for use. In those studies evaluating the use of ECMO, four -- massive or saddle pulmonary emboli, primary pulmonary hypertension, pulmonary parenchymal disease, and COPD -- were identified. Acute onset refractory cardiogenic shock, or ARCS, had the most studies, all of them case series. Acute respiratory distress syndrome, or ARDS, and ARDS due to H1N1 infection had the second largest number of studies identified, including a meta-analysis of three studies: the CESAR trial and two cohorts of patients with ARDS from H1N1 infection.

I would like to start presenting the results on ECMO use due to failure to wean from cardiopulmonary bypass. One case series study reported 38% survival to hospital discharge among 50 patients. Major causes of death included multiple organ failure, sepsis, and cerebral hemorrhage. This study reported transfusion, bleeding, and liver failure as the three most common complications in patients.

There were 10 case series studies assessing ECMO use among patients with acute onset refractory cardiogenic shock. Survival to hospital discharge among these patients was between 24 and 71%. Of these studies, three studies reported survival to one year or more, with Wang and colleagues reporting a survival at four years of 52%. Change of ECMO oxygenator was reported in three studies in 9 to 18% of patients.

The use of ECMO for CPR was found in four studies that reported survival to hospital discharge between 19 and 56%. In particular, a case-control study with 60 matched patients from South Korea reported significantly higher survival among patients that received ECPR compared to CPR. The proportion of patients without neurologic impairment among ECPR recipients was also higher compared to CPR recipients for in-hospital and at six months. The six-month adjusted hazard of mortality or significant neurologic impairment for ECPR recipients was half that compared to CPR recipients.

In a study using ELSO data from nearly 300 patients that received extracorporeal CPR, survival to hospital discharge was 27% for the study period of 1992 to 2007. Survival for the 2000 to 2003 period was higher compared to any of the other periods. Overall, 33% of patients suffer neurologic complications, with the most common cause being brain death. The incidence of brain death was higher for the most recent time period.

Seven articles were identified with relevant data on the use of

ECMO for ARDS in adults: one meta-analysis, one randomized clinical trial, and five case series. Survival to discharge reported in this study ranged from 45 to 84%, and the ECMO circuit complications reported were thrombosis of oxygenator in two studies and failure of pump head in one study of 60 patients.

Here are the results of the meta-analysis of the CESAR trial and two cohort studies. The patients included in the analysis had acute respiratory distress syndrome from pneumonia or H1N1 infection. The CESAR trial and one of the cohort studies conducted the primary analysis by intention to treat. The main pooled analysis excluded patients that did not receive ECMO as a treatment so that there were 179 ECMO patients and 174 non-ECMO. In-hospital mortality among patients that received ECMO in these studies ranged from 24 to 50% whereas the mortality among non-ECMO patients ranged from 40 to 50%.

This figure presents the forest plots with the odds ratio and 95 confidence intervals of the studies used and the pooled results from the main analysis. The pooled odds ratio for in-hospital mortality was 0.71 for ECMO patients when compared to those that did not receive ECMO. The confidence interval for this result is wide and includes 1.

ECMO use for the treatment of ARDS due to H1N1 infection in adults was identified in two cohorts and five case series. One of the case series used data from the ELSO registry. The survival to hospital discharge

reported in these studies ranged from 36 to 92%. For the ELSO registry, the survival was 67% among 237 H1N1 infected adults during August 2009 and March 2010. Two studies reported that 53% and 62% of their patients had one or more ECMO-related complications. Other ECMO circuit complications included cannula site infection and/or septicemia, cannulation complications, oxygenator failures, and blood clots.

The use of ECMO in patients with pneumonia was identified in one case series study from South Korea. The reported survival to hospital discharge in one year was 33% among 12 liver transplant patients. In this study, the major cause of death was multiple organ failure due to sepsis. Two case series studies among U.S. patients with graft dysfunction after lung transplantation reported survival to hospital discharge of 69 and 82%. Survival rates at 30 days, one year, and five years were 82, 64, and 49, respectively, among 28 transplants.

This table presents the results for survival to hospital discharge for the studies included in this literature review. Survival to hospital discharge in patients that had ECMO for failing to wean from cardiopulmonary bypass was 38%; the survival to hospital discharge for patients with acute onset refractory cardiogenic shock, or ARCS, ranged from 24 to 71%; and for the use of ECMO for CPR, it was between 19 and 56%.

For acute respiratory distress syndrome, or ARDS, the survival to hospital discharge ranged from 45 to 84%, and for ARDS due to H1N1

infection, from 36 to 92%. The survival to hospital discharge among patients with pneumonia and placed on ECMO was 33%, and for patients with graft dysfunction after lung transplant, ranged from 69 to 82%.

Overall, four studies compared the use of ECMO with non-ECMO concurrently. Statistically significant differences in safety and effectiveness were observed between the treatment types in one study evaluating extracorporeal CPR. No statistically significant differences in safety and effectiveness were observed between the treatment types in the main analysis of the pooled results of the ARDS studies.

With this, I'm ending my presentation, and I would like to present Dr. John Laschinger, who will present the clinical review of ECMO use for cardiopulmonary failure.

DR. LASCHINGER: Hello. My name is John Laschinger. I'm a medical officer in the Structural Heart Device Branch at FDA. I'm also a board-certified cardiac surgeon who has a UNOS certification for transplant surgery and fellowship training in pediatric cardiac surgery as well.

For the purpose of this discussion, FDA has organized adult cardiogenic shock and heart failure into three general categories based on etiology, rapidity of onset, and the appropriate therapeutic modes of cardiopulmonary or ventricular support required for therapy. These include acute catastrophic cardiogenic shock, subacute cardiogenic shock or heart failure, and chronic progressive heart failure. For all three categories,

standard of care therapies are directed at the underlying cause. Depending on the underlying cause and the mode and rapidity of onset, therapy may include a multitude of combinations of standard therapies. Historically, the majority of ECMO use for primary cardiac etiologies has been in the setting of acute catastrophic cardiogenic shock, which includes post-cardiotomy cardiogenic shock, or failure to wean, and ECMO-supported cardiopulmonary resuscitation, or ECPR.

It should be noted at the outset of this discussion that use of devices such as percutaneous or durable VADs to provide hemodynamic support as part of a therapeutic strategy or to provide temporary or prolonged mechanical support bridging or destination therapy for the prevention or treatment of acute, subacute, or chronic heart failure requires premarket application for approval, and these are not the subject of this classification discussion.

These PMA devices are generally used in the treatment of subacute or chronic progressive heart failure. For these types of heart failure, the clinical deterioration, though severe, is generally non-catastrophic in onset, allowing treatment to occur under more controlled circumstances. Right and/or left heart failure may predominate, and pulmonary function may be acutely or chronically compromised, but usually, a secondary effect that is treatable with standard invasive or noninvasive ventilation and pharmacologic measures aimed at optimizing pulmonary function and

hemodynamics. With the availability of other more appropriate therapeutic device options for advanced heart failure, ECMO therapy is primarily reserved for episodes of acute and unpredicted clinical decompensation, which results in acute catastrophic cardiogenic shock.

What we are discussing today is acute catastrophic cardiogenic shock, which is characterized by some unexpected primary cardiac events which are catastrophic in nature. The underlying cardiac injury, which may or may not be reversible, typically results in diffuse global cardiac injury with acute loss of pump function and secondary acute pulmonary failure due to a lack of forward flow through the lungs, pulmonary edema, or a combination of the two.

The typically diffuse nature of global cardiac injury may be temporary, due to myocardial stunning, or permanent, resulting from local or diffuse sub-endocardial or full thickness myocardial necrosis. In these often uncontrolled settings, death is imminent, and immediate treatment directed at stabilization of both organ systems is indicated, with later determination of the specific needs for each system as the patient's condition stabilizes.

Due to the typically global nature of the underlying cardiac insult for these two entities, all available standard medical and device therapies may be quickly exhausted, and immediate death is an unavoidable outcome without rapid restoration or augmentation of cardiopulmonary function by artificial mechanical means using ECMO. We will now briefly

summarize the overall historical outcomes of ECMO therapy for these two entities, starting with post-cardiogenic shock, followed by ECPR.

Risk factors for development of post-cardiotomy cardiogenic shock requiring ECMO in the Cleveland Experience Clinic for adult patients operated on from September 1992 to January 2000 are summarized on this slide. Significant demographic, clinical, cardiac, and experiential risk factors were identified as shown. Unmeasurable risk factors such as the adequacy of myocardial protection, cardiopulmonary bypass, and the surgical procedure may also play a role.

A meta-analysis by Cheng et al. summarizes reported survival to discharge data highlighted in red from numerous series of adult patients undergoing ECMO for post-cardiotomy cardiogenic shock and cardiac arrest indications. In this meta-analysis, ECMO use for post-cardiotomy cardiogenic shock has shown a range of survival outcomes. Disparate results between individual centers are evident due to, among other factors, difference in patient mix and indications, varying thresholds for decision to institute ECMO, and varying experience in the care patients requiring ECMO both while on support and post-weaning. In general, for post-cardiotomy cardiogenic shock, it can be expected that approximately 50 to 70% of patients will wean from ECMO, and 35 to 50% will be discharged alive.

The Extracorporeal Life Support Organization, or ELSO, registry is a voluntary registry open for patient entry to all centers with ECMO

programs. Survival data for patients undergoing extracorporeal life support reported to the ELSO registry by age and indication between 1990 and 2013 corroborate the approximately 40% survival for post-cardiotomy shock seen throughout the literature.

Neurologic, renal bleeding, and hemorrhagic complications of ECMO and limb complications of peripheral cannulation are significant sources of major morbidity in the acute phase. Major disadvantages of ECMO are the need for anticoagulation and the requirement for high amounts of transfused blood products, which increases the systemic inflammatory response that is induced by the initial surgery, ECMO components, and cardiogenic shock itself. ELSO data and clinical experience has shown that rapid recovery of cardiac function consistent with life and the adequacy and duration of ECMO support are the primary determinants of the ability to successfully wean from support in the acute phase.

In summary, the cumulative literature has shown that high mortality has continued to plague prolonged cardiopulmonary and circulatory support with ECMO in the post-cardiotomy setting. Despite progress in intensive care management and in ECMO hardware components, in-hospital mortality has not significantly changed during the past two decades.

Separate analyses of post-cardiotomy cardiogenic shock patients undergoing ECMO at the Cleveland Clinic in two distinct time periods, 1992 to 2000 and 2005 to 2010, showed no difference in overall

successful wean or bridge to VAD or transplant rates in the two respective time periods. And overall survival to discharge in ECMO patients in these two time periods were also identical.

Although advances in technology have been effective in easing the ability to care for these patients, overall wean and survival rates are unaffected by different manufacturer components and combinations of centrifugal pumps and hollow fiber oxygenators. Due to the exponential increase in complications with time and the rarity of cardiocirculatory recovery after five to seven days of ECMO support, forced ECMO weaning or transition to a durable VAD after a 48- to 72-hour interval is usually recommended.

The strategy of ECMO support for failed conventional CPR has evolved following reports of poor outcomes for adults treated by standard CPR. Data from 14,720 events entered into the National Registry of Cardiopulmonary Resuscitation showed a survival rate of 17% for in-hospital cardiac arrest. The important factors identified as predictors of poor outcome from the registry patients are listed on this slide.

The most important of the numerous factors which confound the ability to compare or combine results from various studies of ECPR are summarized on this slide. In an attempt to decrease this poor survival, ECMO-supported CPR has been variably applied to several patient populations. As a result, selection bias plays a large role in all available

comparisons, and the ultimate value of ECPR as a proven therapeutic strategy for failed, prolonged CPR in adults is largely unknown. Although not listed, a further confounding factor is the personnel cost requirements of maintaining trained, onsite 24/7 ECPR team, which limits universal availability even in specialized cardiac centers.

Chen et al. performed a three-year prospective observational study on patients age 18 to 75 with witnessed in-hospital cardiac arrest of cardiac origin undergoing conventional CPR more than 10 minutes. Outcomes in patients where ECPR was initiated at some point after this time point were compared to outcomes in patients receiving continued conventional CPR. Data from the unmatched cohort show survival to discharge was significantly higher for the ECPR patients. Longer CPR duration was associated with poor prognosis, and ECPR was protective at all time intervals up to 60 minutes following the onset of failed conventional CPR. Multivariate analysis showed that factors associated with survival to hospital discharge include the presence of a favorable ventricular dysrhythmia, use of ECMO assistance, and lesser duration of CPR.

The prospectively planned propensity score matching process was then selected in 46 patients from the ECMO-supported group and 46 from the conventional CPR group for further analysis. Survival to discharge was significantly higher in the matched extracorporeal CPR group compared to conventional CPR. For survivors, greater neurologic outcomes showed no

difference at discharge. The Kaplan-Meier plot showed better survival in the extracorporeal CPR group at the end of 30 days and at one year. The comparison of hazard ratios for these matched cohorts favored ECMO-supported CPR over conventional CPR at all time intervals.

Two subsequent propensity matched studies by Shin and Maekawa have corroborated the significant survival benefits for ECPR-treated cohorts. Notably, patients in the Maekawa analysis were patients with out-of-hospital cardiac arrest.

In a meta-analysis of all available observational studies for ECMO use following cardiac arrest from various causes, Cardarelli et al. found that the overall survival to hospital discharge reported in the literature was 40%, mean time of CPR prior to ECMO initiation was 40 minutes, and there was a trend to better survival for patients with less than 30 minutes of CPR prior to ECMO. Median ECMO run was 54 hours, and when evaluated by quartiles of duration of support, those who were able to be weaned or transition to more durable devices prior to 2.5 days of support displayed a trend towards higher survival, 61%, with lower odds ratio for mortality compared with the rest.

Factors associated with improved survival for the 295 ECMO-supported CPR patients entered into the ELSO registry from 1992 to 2007 are summarized in this slide. More liberal use of ECPR in adults over time has not resulted in improvements in survival, and ELSO registry data for adult

patients treated with ECPR found a significant trend towards increased mortality in recent years. Additional literature reports of survival to hospital discharge in patients undergoing ECPR fall within a relatively consistent range of approximately 25 to 45%, consistent with the 27% overall survival seen the ELSO registry.

Neurologic injury during ECMO precludes good outcomes among patients who are supported for any indication. In patients using ECPR, the risk of central nervous system injury following CPR may be added to the risk of CNS injury posed by the ECMO support. Analysis of ELSO data found that 33% of patients undergoing ECPR had post-procedure diagnoses of CNS injury, and 21% met criteria for brain death. Patients meeting brain death criteria were withdrawn early from ECMO. Whether brain death in these patients occurred during CPR or during ECMO is not certain. For out-of-hospital cardiac arrest, Maekawa et al. identified pupil dilatation greater than 6 mm at the time of hospital arrival as a significant predictor for poor neurologic outcome following ECMO-assisted CPR.

In summary, aggressive use of ECMO-assisted CPR has resulted in improved salvage versus conventional CPR. Reversible and treatable cardiac causes fare better, and predictors of worse outcome include high lactate levels pre-ECMO and renal failure, neurologic injury post-ECMO-supported CPR. The duration and effectiveness of CPR is predictive of mortality and survival in both series. And increasing use over the last decade

has not resulted in improved survival over time.

When considered as a whole, acute catastrophic cardiogenic shock resulting in pump failure and/or cardiac arrest are conditions incompatible with life, which result in a need for acute restoration of cardiopulmonary function. Efforts to determine the cause of underlying failure at this point become secondary, and all treatment alternatives have to be assessed in light of an otherwise dismal prognosis.

As a therapeutic strategy in these circumstances, early decision and institution of ECMO is essential. ECMO used in these circumstances results in a low but predictable rate of salvage that is not achievable using standard of care therapy. ECMO fits with almost all patients and clinical scenarios offering varying cannulation options and covers abnormalities in biventricular function and lung function.

ECMO can provide short-term circulatory support, but allows bridging of patients for further evaluation and decision making and judgment of neurologic status. As a result, ECMO may serve an important role as an acute rescue modality in patients with primary cardiac disease presenting with acute cardiogenic shock or cardiac arrest.

Given the lack of effective alternative treatments and the alternative outcome of almost certain death without therapy, there is no equipoise for clinical evaluation of ECMO when used for these specific purposes. Even if it were possible, the consistency of available anecdotal

reports over decades of use do not suggest rigorous trials designed to specifically determine outcomes of ECMO use for these indications will yield results different from those already observed in the literature.

Thank you. And now Maria Jison will discuss the pulmonary indications for ECMO.

DR. JISON: Good morning. My name is Maria Jison. I'm a medical officer in the Respiratory Devices Branch. I'm board certified in pulmonary critical care medicine and still practice part time as an intensivist. I'll be presenting additional discussion of the evidence for ECMO for the treatment of specific pulmonary indications.

First, I'm going to begin with a brief discussion of ARDS etiology, epidemiology, and definitions. Then I will discuss the standard of care in the treatment of severe acute respiratory failure and ARDS. Lastly, I'll discuss in more detail what Dr. Avila-Tang had touched upon with regards to the evidence for ECMO use in the treatment of ARDS and other respiratory indications, with specific focus on the limitations of the studies.

ARDS is a distinct type of respiratory failure characterized by alveolar flooding, atelectasis, decreased lung compliance, and severe gas exchange abnormalities. ARDS complicates a variety of illnesses. ARDS due to varying etiologies results in the same clinical, physiologic, and pathologic features. The management of ARDS is the same regardless of the inciting event.

The incidence of ARDS was determined in a multicenter, population-based prospective cohort study back in 2005. Based on this study, which followed over 1,100 patients with ARDS for 15 months, approximately 10 to 15% of admitted ICU patients and up to 20% of mechanically ventilated patients met criteria for ARDS.

After the initial description of ARDS in 1967, multiple definitions were used until the 1994 American-European Consensus Conference, or AECC, definition was published. The AECC defined ARDS as the acute onset of hypoxemia with bilateral infiltrates on chest x-ray with no evidence of left atrial hypertension as measured by pulmonary capillary wedge pressure. This definition was widely adopted and led to the acquisition of a wealth of data which has led to improvements in the care of ARDS.

In 2012, a consensus conference was held where new trial data were considered, and the AECC definition of ARDS was revised to the new Berlin definition, which is seen on this slide. New features of the Berlin definition includes grades of ARDS and that congestive heart failure patients can also have concurrent ARDS, and thus, a wedge pressure less than 18 was no longer a requirement, although objective assessment of heart function, such as echocardiogram, was recommended. Having said that, the majority of studies included in our literature review were conducted based on the 1994 AECC definition.

The standard therapy for severe acute respiratory failure and ARDS include supportive care, oxygenation, and treatment of the underlying inciting conditions. Care is usually provided in an intensive care unit setting. The majority of ARDS patients require mechanical ventilation. Adjunctive strategies may include novel therapies such as prone positioning and vasodilators such as nitric oxide.

With respect to mechanical ventilation, there was a significant change in the ventilator management of ARDS, which took place around 2000 as a result of the ARMA trial. Prior to this trial, mechanical ventilation was typically delivered using tidal volumes ranging from around 8 to 10 to 15 mL/kg. The ARMA trial marked a turning point in the ventilator management of ARDS. This trial was a randomized controlled study which demonstrated reduced mortality in ARDS patients randomized to low tidal volume defined as 6 mL/kg, shown in this graph in gray bars, and compared to conventional ventilation defined as a tidal volume of 12 mL/kg, shown in black bars. Mortality in the low tidal volume group was 31% versus 40% in the high tidal volume group. Subsequent meta-analyses have also demonstrated improved 28-day and hospital mortality.

Since the publication of this trial, a lung protective ventilation strategy using smaller tidal volumes has become the standard of care for mechanical ventilator support and ARDS. Despite this important advance, ARDS still represents a treatment challenge, and rescue or adjunct therapies

are still needed in up to 35% of patients. It is because of this change in the standard of care that we focused our literature review to studies after the year 2000.

Now let's turn our attention back to ECMO. There is limited data in the literature regarding the use of ECMO for adult pulmonary indications. Before 2000, there were only two randomized control trials that evaluated the use of ECMO in severe acute respiratory failure or ARDS. Zapol and colleagues in 1979 conducted a prospective randomized study in nine centers to evaluate prolonged ECMO as a therapy for severe acute respiratory failure. The majority of patients suffered acute bacterial or viral pneumonia. Ninety adult patients were randomized to either conventional mechanical ventilation or mechanical ventilation supplemented with partial veno-arterial bypass.

This slide shows survival out to 30 days for the ECMO group, in white circles, versus the control group, in black circles. Only four patients in each group survived. The majority of patients died of progressive impairment in gas exchange and compliance. The authors concluded that ECMO can support respiratory gas exchange but did not increase the probability of long-term survival in patients with severe acute respiratory failure.

Morris and others, in 1994, evaluated the impact of pressure-controlled inverse ratio ventilation followed by extracorporeal CO_2 removal on the survival of patients with severe ARDS in a randomized controlled

clinical trial. Forty patients with severe ARDS were randomized to ECMO. The main outcome measure was survival at 30 days. As you can see from this slide, survival was not significantly different in the mechanical ventilation patients, shown in the dark line, compared to extracorporeal patients, represented by the dashed line. The survival in controls was slightly better, at 42%, versus ECMO patients, who fared worse, at 33%. Extracorporeal treatment group survival was not significantly different from other published survival rates after extracorporeal CO_2 removal. The authors concluded that there was no significant difference in survival between the mechanical ventilation and the extracorporeal CO_2 removal groups. The authors did not recommend extracorporeal support as a therapy for ARDS and stated that extracorporeal support for ARDS should be restricted to controlled clinical trials.

As Dr. Avila-Tang noted earlier, there have been few studies in the last 15 years evaluating the use of ECMO for pulmonary indications. The majority of studies have been in the last six to seven years, with a resurgence during the H1N1 influenza pandemic. Seven articles were identified with relevant data on the use of ECMO for ARDS in adults, including one meta-analysis, one randomized controlled trial, and five case series. Survival to discharge ranged from 45 to 84%. There has been only one randomized controlled trial of ECMO for severe ARDS since the studies by Zapol and Morris. And this was the CESAR trial. For ARDS specifically due to H1N1

influenza and the use of ECMO, there were seven studies, most of which were case series. The next few slides will discuss the strengths and weaknesses of the individual studies evaluating ECMO and ARDS.

The bulk of the data in general and on ARDS come from these next few slides. This slide shows results from the meta-analysis of ECMO for ARDS conducted by Zampieri, which includes three studies. The CESAR study is the only randomized controlled trial of ECMO for ARDS mostly due to pneumonia. The Noah and Pham studies evaluated ECMO for H1N1-associated ARDS compared to propensity score matched controls.

The authors also conducted the meta-analysis in three different ways. The first analysis method looked at only those patients who received ECMO from all three studies and propensity score control matching method without replacement. This analysis did not demonstrate a mortality benefit in the ECMO group compared to the non-ECMO group.

The second analysis excluded the 33 patients from the CESAR trial and the Noah study who were transferred for but did not actually receive ECMO therapy. This analysis used the propensity score matching of controls method with replacement. The results of this second analysis demonstrated an ECMO mortality benefit which was statistically significant.

The third analysis included subjects from all three studies, including the 33 from the CESAR and Noah studies which were referred but not treated with ECMO. Controls were again matched using propensity score

with replacement. On this analysis, ECMO was associated with a reduction in hospital mortality that was also statistically significant.

The CESAR trial was conducted in the UK, and all ECMO patients were referred to a single expert treatment center. Out of the 90 patients that were randomly allocated to ECMO, 75% actually received ECMO treatment, but 25% did not. The figure on the left shows the survival curve for ECMO-referred patients and the control ECMO non-referred in the dashed blue line. Six months survival was much better among the ECMO-referred patients compared to those that received conventional ventilation. The table on the right demonstrates that ICU and hospital length of stay for the ECMO-referred group was longer.

While the CESAR trial demonstrated reduced mortality in the ECMO-referred group, it is notable that 25% of patients that were referred to the ECMO center did not actually receive ECMO. The better outcome may reflect some referral center bias. Another limitation of this trial was the lack of standardization of the conventional ventilation arm, which was conducted at separate centers from the ECMO arm. Since the positive results of this study, the enthusiasm for ECMO experienced somewhat of a resurgence especially during the 2009 H1N1 influenza pandemic.

The next few slides will discuss the other two studies from the meta-analysis, which was in H1N1.

Noah and others evaluated ECMO-referred patients and

compared them to historical matched controls. The control matching was performed using three different statistical approaches, which all led to similar results. This is a survival curve from the Noah study using the propensity score matching method. The hospital mortality rate was roughly half the rate for ECMO-referred versus non-referred patients. As with the CESAR trial, there may be some element of referral bias, because 11 of the 80 referred patients, or 14%, in the Noah study did not receive ECMO.

Other limitations of this study are that the non-ECMO-referred patient group may have had more severe disease in that they were judged to be too sick for ECMO. While the matching attempted to compensate for this, matching variables were limited. Second, like the CESAR trial, management of non-ECMO-referred patients was not part of the study's protocol. It was not possible to determine whether lung protective ventilation was used in the controls.

Pham and colleagues evaluated patients treated with ECMO for H1N1-associated ARDS in French ICUs between 2009 and 2011 using data from a national registry. The authors also compared results to propensity score matched controls. Before matching, 103 patients who received ECMO were compared with 157 patients who had severe ARDS criteria but did not receive ECMO. ICU mortality before control matching was similar between the ECMO and non-ECMO groups. Matching controls using the propensity score without replacement method reduced the number of unique pairs for

comparison to 52. Using this conservative control matching method, the authors also found that there was no significant difference in ICU mortality.

The strengths of this study are that it looked at only ECMO-treated patients and used propensity score matching without replacement. Like the Noah study, a limitation of the Pham study is that patients treated with ECMO had less severe disease. ECMO subjects were younger, included a higher proportion of pregnant women and obese patients, had less comorbidities, less immune suppression, less bacterial infection on admission, and a lower proportion received early steroid treatment.

I would like to discuss some of the limitations of the matching method for historical controls, as was done in the Noah and Pham studies. Propensity score matching may not control for all confounders and carries a risk of unrecognized imbalance in baseline severity. There are important methodological differences between the Pham and Noah studies. Pham included more covariates in the propensity scoring and used more stringent matching parameters, for example, matching without replacement. To explain the differences from the Noah study, Pham and colleagues repeated the matching of their own study using different techniques. In a complementary propensity score analysis of their own data using a matching procedure with replacement similar to that used in the Noah study, Pham found that treatment with ECMO seemed to be associated with a significantly lower risk of death, which was consistent with the Noah results.

While the Noah study reported better outcomes for ECMO, the Pham study reported no benefit. Many of the ECMO and control patients in the Pham study were managed concurrently in the same centers. In contrast, the Noah study, as well as the CESAR trial, transferred the ECMO patients to a referral center, and so these two studies may have suffered some referral center bias.

Age is a significant potential confounder particularly in the above case series of H1N1 ECMO therapy. The ECMO-treated H1N1 patients from both the Noah and Pham studies tended to be younger and were more likely to survive solely due to age.

The rest of the data on ARDS and ECMO are quite limited. Linden evaluated long-term data of ARDS ECMO survivors in Sweden. Outcome data included survival to hospital discharge and beyond of 37 ECMO patients. All patients were healthy prior to the ARDS ECMO episode. This study demonstrated a high survival rate to hospital discharge of 70%, and the majority of survivors were able to return to work in the same occupation as before ECMO. Mean values for lung spirometry and exercise performance tests were in the low normal range. Respiratory quality of life scores suggested subjective respiratory problems with impacts on daily life. While this study offers a window into the long-term effects of ECMO on survivors, the sample size is quite small.

Other smaller studies of portable or miniaturized ECMO for

ARDS by Muller and Haneya demonstrated high rates of survival but significant mortality due to multi-organ failure. There was a high rate of ECMO circuit complications in the Haneya case series. Surgical site bleeding and thrombosis of the oxygenator were observed in the Muller study. Both studies are limited by their small size and heterogeneous populations with respect to etiology of ARDS. The Muller study also lacked a control comparison. As with the CESAR trial, there may have been some bias related to transport to an expert center.

So just to summarize briefly for ARDS, the evidence for the use of ECMO in ARDS has several limitations with mixed results. For the cohort studies and meta-analysis, the mortality benefit and significance vary depending on the type of control matching method used.

Let's now look at the H1N1 influenza indication. As already noted by Dr. Avila-Tang, the data for ECMO use for ARDS due to H1N1 in adults demonstrated improved survival. However, caution must be taken when interpreting these results. Patients with H1N1 who became ECMO-referred patients were not representative of all patients with H1N1. As already noted in the Pham and Noah studies, ECMO-referred patients were younger and received longer durations of mechanical ventilation, including use of alternative ventilation strategies, compared with eligible non-ECMO-referred patients. The survival benefit associated with transfer for ECMO could be attributed to other factors associated with specialized, highly

resourced, and experienced centers. In addition, the Noah and Pham studies demonstrated conflicting results despite both using rigorous propensity score matching of controls.

The other case series from Italy did not have a comparison to a matched control population. Other case series studies in our literature review had very small sample sizes, less than 15, and reported survival to hospital discharge rates ranging from 36 to 92%. ECMO can be associated with numerous complications, as Drs. Avila-Tang and Laschinger have already noted. The Takeda study from Japan noted that all 12 facilities that administered ECMO treatment had limited experience with ECMO and that there was a 93% rate of ECMO-associated adverse events in that Japanese study.

Let's look at the evidence for ECMO in pneumonia. The CESAR trial included 62% of subjects with ARDS due to pneumonia of various etiologies. While the CESAR trial demonstrated a mortality benefit compared to conventional therapy, the limitations of the study have already been noted.

One small case series from South Korea evaluated the use of ECMO for respiratory failure due to pneumonia or ARDS in patients who received orthotopic liver transplant. This study had a high mortality rate with a major cause of death being multi-organ failure due to sepsis.

Shaffi and others evaluated the use of ECMO as a bridge to

lung transplant in 19 patients, the majority of which were usual interstitial pneumonia patients. Fourteen, or 74%, were successfully bridged to transplant using both veno-venous and veno-arterial ECMO. The rest of the patients died either before transplant or after double- or single-lung transplant. ECMO-bridged patients experienced a considerably higher rate of major complications and had longer hospital courses post-transplant. The current evidence is limited for the indication of bridge to transplant, and the long-term outcomes of ECMO in this patient population remain uncharacterized.

Hartwig evaluated the use of ECMO for post-lung transplant primary graft dysfunction; 28 of 498 transplant recipients received veno-venous ECMO. Survival is quite good, although allograft function at three years was significantly worse in the ECMO-treated recipients versus controls. However, the study was a retrospective study. In addition, the patients who required ECMO had a higher rate of requiring cardiopulmonary bypass during the transplant operation. This study could be considered more of a study of failure to wean off cardiopulmonary bypass intraoperatively, which we have categorized under cardiopulmonary indications. Notably, the ECMO group had a high rate of bacterial blood stream infections, 35% versus 12%, which was statistically significant.

In summary, there have been few studies with several limitations to date of ECMO in adult respiratory failure and ARDS, the

majority of which are only case series. ECMO can be associated with device-related complications. The long-term outcomes in adult survivors of ECMO therapy for ARDS remain poorly characterized. The current evidence in is inconclusive regarding the benefits of ECMO for adult respiratory failure.

While the results of the Zampieri meta-analysis suggests a mortality reduction for ARDS ECMO-treated patients, the confidence intervals from the main analysis were wide and spanned unity, and the individual studies included in the analysis had several limitations, as already noted.

In addition, the majority of the studies evaluating ECMO use for the indications for use assessed in our literature review were case series and did not include control groups. ECMO patients are already at high risk for death due to other complications, and the lack of a control comparison makes data interpretation difficult. Only the CESAR trial was a randomized controlled trial, where approximately 60% of subjects in both arms had ARDS due to pneumonia, and as already noted, significant confounding issues impact the interpretation of those results.

For H1N1-associated ARDS, the data are suggestive that there may be equipoise for ECMO. However, caution must be used in generalizing results from the limited studies.

One last note. We wish to reiterate that our reclassification efforts will result in a final classification for ECMO that will be appropriately based on the level of evidence and risk/benefit profile discussed today and at

the September 2013 panel meeting. The classification will affect how a device will be cleared or approved for marketing and ultimately how the device will be labeled and promoted. However, the FDA does not regulate the practice of medicine, so physicians will still be able to continue to use ECMO to treat patients as they see necessary.

Thank you.

DR. HIRSHFELD: So thank you. I'd like to thank Ms. Wentz and Dr. Avila-Tang, Dr. Laschinger, and Dr. Jison for a very detailed and information-packed and comprehensive presentation. So thank you very kindly.

Before we move to the next step, I'd like to inquire whether any of the Panel members have any brief clarifying questions for any of the FDA presenters. There will be ample opportunity later on to dig into these concepts and question the FDA, Panel members, in depth later on.

Yes, Dr. D'Agostino?

DR. D'AGOSTINO: Just to make sure, in propensity score analysis, the term "with replacement" has different meanings to different people. Could you be explicit in what was the use in these particular meta-analyses -- I mean propensity analyses?

DR. JISON: I think --

DR. HIRSHFELD: Please identify yourself.

DR. JISON: Maria Jison, medical officer, FDA. I was referring

mostly in those comments to the Pham and Noah studies where the "with replacement" means that the controls, once they were matched to an ECMO subject, could be placed back into the pool and used again.

DR. D'AGOSTINO: That's the standard. Sometimes it's a variation of that --

UNIDENTIFIED SPEAKER: Your mike, please --

DR. D'AGOSTINO: Yeah, that's the usual, but sometimes there's a variation of that, so I think your presentation was very substantial in the identification of issues.

DR. HIRSHFELD: Dr. Brindis?

DR. BRINDIS: Ralph Brindis. Just two questions. In terms of the FDA pediatric hearing, in terms of special controls recommended, it was not -- I didn't see listed the utilization of registries, and so I'd be interested in that comment. And also, on slide 20, when we have the MDR reports, I don't have an idea about the actual volume utilization of ECMO in the United States and what -- do we have an idea on that and their temporal changes over time?

MS. WENTZ: Catherine Wentz, FDA. So to answer your first question regarding the registries, the special controls are currently defined very broadly, and the registries will be included in the special controls. We will be able to use the data in the registries as the special controls if you see that that's needed or appropriate.

Regarding the volume of ECMO, since ECMO is not cleared as a circuit, we really can't track how many ECMO procedures are performed. It's used off-label. The MDR process is voluntary. So I personally, not being a clinician either, I think you all probably have a better idea as to the volume of ECMO than we do.

DR. BRINDIS: Just to be clear, was the recommendation of the pediatric panel to utilize registries, and we don't have CPT coding for ECMO to be able to get an idea of the volume?

MS. WENTZ: So the pediatric one, again, the same special controls were identified for the pediatric one, and I do believe that the registry -- that there was a brief discussion on the use of registry data at that time. So, for example, if we reclassified for certain indications, and if a device wants that labeling, and they've got significant data in the ELSO registry, they can use that data to support their 510(k).

DR. LASCHINGER: And in the ELSO registry, which is the best data we have as far as the use goes, there's been about 55,700 uses since 1990 to 2013, period. Most of those -- over half of them have been in the neonatal age group, with the remaining being in the pediatric and adult age groups. Total adult age group use is about 9,000 for adults for the various uses over that period of time.

DR. HIRSHFELD: Dr. Cigarroa?

DR. CIGARROA: This is a question to clarify slide 39 in FDA

presentation by Dr. Tang. Could you bring up that slide? This is in reference to the ELSO registry. It is stated that survival was 27% and that neurologic complications were 33%. I simply wanted a clarification. Are those neurologic complications of the overall registry, inclusive of patients that survived and died?

DR. AVILA-TANG: This is Dr. Avila-Tang. Yes, I believe so. Of those that, among the adults, that they have survival complications, specifically on the majority where the brain death, so that was 21%.

DR. LASCHINGER: Yeah. I covered the same publication, and yes, it was 33% in all-comers, whatever you want -- in all patients of whom 21% of the total had brain death and were -- had a forced wean or early wean from ECMO. John Laschinger. I'm sorry.

DR. HIRSHFELD: Yeah. I see there are other Panel questions. I'd like to stay on schedule. We're going to have other -- we have ample time to discuss this and bring these up later on, so I think please hold your questions for the moment, because I'd like the schedule next to get to the Open Public Hearing.

Thank you to the FDA panel, and we'll now move to the Open Public Hearing.

So we'll now proceed with the Open Public Hearing portion of the meeting. Public attendees are given the opportunity to address the Panel and to present information or views that are relevant to the meeting agenda.

And Ms. Waterhouse will now read the Open Public Hearing disclosure process statement.

MS. WATERHOUSE: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. HIRSHFELD: Okay. Thank you. So we've received communications from five individuals who indicated a desire to speak. The first person will be Dr. Corey Ventetuolo. Is she here? She's not here? She was not able to come, okay.

Next person is Dr. William Lynch. And you have five minutes.

And just for all the public speakers, please announce your name and your affiliation and also any affiliation you may have with any of the entities presenting today.

DR. LYNCH: So thank you for the opportunity to speak. My name is William Lynch. I come representing the ELSO organization that you've already mentioned. I've been chairman for the past two years. I have no financial conflicts. In addition to being chairman, I'm also a thoracic surgeon. I've been practicing ECMO and did an ECMO fellowship for over 15 years. I've started one program, helped start three others, one in South Africa.

The data, I think, is difficult to interpret, so I'd like to comment on that. I'd like to comment on the fact that ECMO really should not be considered a therapy. It should be considered a mode of support. And I would like to comment on the status today, which is respiratory support, which is growing significantly in the United States as well as across the world.

This is a picture of the data as it currently exists. Although it's a cluttered slide, the things that are important to notice is that we break it down into three categories, so it's broken down into neonatal, pediatric, and adult. And then with each category, there is respiratory, cardiac, and CPR. And probably the most important thing to recognize is looking down this list of survival to discharge is the percentages of survival are very different. And the reason that's different is the patients are different, their pathophysiology

is different.

So the panel that met in September talking about neonatal support; an example that was given is that 90% survival in meconium aspiration in the setting of ECMO, which is true. In adults, the data that was quoted was 50% survival in adults at that time, which is also true. However, adults are not just big babies. They're very different. The thing that's important to recognize, too, also, about meconium aspiration is that even though it's 90% survival in the setting of ECMO, that's very rarely used anymore in meconium aspiration. And the reason that's the case is that meconium aspiration now can be supported with oscillator ventilators and nitric oxide. Those therapies are not effective in the adult patient population.

Another study to comment on is -- or at least two studies that were mentioned today, the Morris study, and the Zapol study of adult respiratory failure in ECMO, stating that the Zapol study showed a 10% mortality, which is -- I'm sorry -- a 10% survival, which is true, but the control arm also had a 10% survival, and that was supported with mechanical ventilation. And although adult ECMO is essentially stopped at that time, we continued to use ventilators. So there is somewhat of a disparity in the technology that is available.

The Morris study also showed 10 years later that there was an increased survival in both arms, 40%, which I think really is a reflection of our improvement in critical care and ventilator management, but also in the

world of ECMO support.

So this is what's going on in the world of ECMO in ELSO centers. So there is a dramatic increase in the number of centers, as you can see from the right side of this graph. These are number of centers in the international registry. I think earlier a question was asked if we know how much ECMO is being done in the United States, and the honest answer to that is no. However, if you look at this particular slide, this is showing adult cardiac ECMO that's growing, and the numbers of growth over the past four years is about fivefold. But what's more important to pay attention to is the growth in adult respiratory is almost tenfold over that same time frame. And so this slide shows almost 1,000 ECMO cases. Over 500 of those have been in the United States in the past year. But if I were to guess, and I can only guess, we're probably only capturing half of the ECMO that's being done in this country. So around 1,000 cases would be my guess per year.

In addition to what was just shown, these are the results broken down by disease category in adult respiratory. And, again, just paying attention to the percent survival on the right, we're showing a survival rate according to our registry of modern ECMO, meaning in the last five years, of 54 to 66%, which is different than what we typically will quote as a survival of around 50%. So the strategy of ECMO is changing. Our patient selection, I think, has improved, and the management with the technology has also improved.

So I can't touch on all of these, but some of the draft questions that were posed to the Panel had to do with some of these risks associated with ECMO technology, specifically the membrane oxygenator, but realizing this is a support that requires a collection of technologies together.

If you look through this list, really looking at maybe the first four on the left side, these are all reflective of membrane technology, most importantly, the preamendment device that is available, the silicone membrane device or the SciMed oxygenator. The technologies that are available now that have displaced that are membrane oxygenators that have a polymethylpentene membrane, and as a consequence of the new technologies, the membrane and the way the oxygenators are built, the risks related to thrombocytopenia hemolysis and other things listed there are dramatically different, much lower.

And, in particular, in the adult patient population, as opposed to pediatric population, the amount of flow that can be driven through these oxygenators, meaning 4 or 5 L per minute, compared to a neonate that might be 500 cc's a minute, the risks of thrombosis and the need and the dependence on anticoagulation has also become very, very different. So, in other words, you can manage these patients without anticoagulation for long periods of time if necessary. And that changes the risk profile both to the patients and from the devices.

So, in summary, there's dramatic growth in adult ECMO in the

United States as well as in the world. This is in all disease entities, respiratory, cardiac, and ECPR. The safety profile of the technologies, most importantly, the centrifugal pump use, the polymethylpentene membranes, and then the adult --

DR. HIRSHFELD: Are you summing up for us, please?

DR. LYNCH: Yes, yes. The adult dual lumen cannulas makes the ability to support these patients for long duration and in a safer fashion practical and possible. The CESAR trial, the H1N1, and the fact that lung transplants are now managing patients with ECMO before and after has also changed the interest in ECMO in this adult patient population.

Thank you.

DR. HIRSHFELD: Thank you, Dr. Lynch.

Our next speaker will be Dr. Joseph Zwischenberger.

DR. ZWISCHENBERGER: Hello. I'm Jay Zwischenberger. I'm Chair of the Department of Surgery at the University of Kentucky. I've been active in the field of ECMO for the last 30 years. I was Bob Bartlett's first ECMO fellow at Michigan, and I helped develop the ELSO group and the registry.

I rise to help you understand some of the dynamic nature of this field. I've had competitive funding through the NIH for the last 25 years. I do have a number of contracts with companies, and I'm the co-patent holder of the Avalon Elite Catheter, which is the current double lumen

catheter used for ambulatory ECMO.

Part of the reason I present is because I am so active in the field, I wanted you to appreciate what the practitioners are doing. I recently gave a summary of ECMO at the American Association of Thoracic Surgeons' meeting literally last week. And I've been invited to give an overview at the Society of Thoracic Surgeons Symposium on ECMO later this month. So what you're hearing is exactly what's happening today.

We currently have embraced the concept of ambulatory ECMO, and in fact, ECMO as a term is a broad breadbasket of a number of activities, including walking ECMO, with a dual lumen veno-venous catheter, walking bypass, with right atrium to AO cannulation such as in patients with biventricular failure, and ambulatory right heart bypass, and those with pulmonary hypertension. This dynamic nature has resulted in numerous algorithms presented at our meetings, including the Red Book. This was written by Shaf Keshavjee from Toronto, and it shows that the whole spectrum of hypercapnic respiratory failure and hypoxic failure can be handled with different iterations of the ECMO technology.

Our group just presented or published in the last several months at the *Journal of Thoracic and Cardiovascular Surgery* our experience with ambulatory ECMO for a bridge to transplantation. Again, much of what you heard was decades old, but this has just been presented. And that is, we have a 93% survival in patients as a bridge to transplant. We started out, as

you saw from the literature, that pump failure from cardiac failure was often an indicator early, but now respiratory failure is our most common indication. In fact, we have gone on record as saying ECMO bridge to transplant or recovery is evolving into standard of care. Our latest results as of last night was 37 of 40 patients have survived to six months in an ambulatory bridge to transplant.

That leads us to even wonder does anybody with severe respiratory failure really benefit from mechanical intubation and positive pressure ventilation because we're seeing with ECMO that we are preventing barotrauma and activation of inflammatory mediators. We're limiting end organ injury. We're avoiding sedation. And we're addressing the very hot topic in pulmonary medicine today, and that is frailty and the development of frailty while on long-term ventilation.

Most notably, our last 15 consecutive ambulatory ECMO'd adult patients are now alive to six months. That's led me to work with industry, the MAQUET Corporation, to further refine the double lumen catheter to make it easier to insert and shorter so that it can be inserted at the bedside and allows patients to ambulate, we think, more safely.

Lastly is a news flash from the International Society of Heart and Lung Transplant from last month. There was a presentation on ambulatory ECMO as a bridge to transplant resulting in a 30% reduction in total cost when compared to non-ambulatory ECMO bridge. And the

adoption of a nurse-driven program to ambulate patients on VV ECMO is now considered safe and reduces other complications that are associated with immobility and progressive frailty.

And, finally, I'll be presenting this later this month at the STS, and that my personal recommendation is that ambulatory catheter-based technology, or ECMO in a broad sense, is indicated in children, neonates, and adults for both acute severe respiratory failure and acute cardiac support, and for transplantation, it's now being utilized to support the recipient, the donor, and in fact, work is being done on lung in a box, which is an organ block preservation.

So I think, most importantly, the dynamic nature of this field should be appreciated. I've been in it for 30 years. I've been involved with much of the literature that was presented here today. And I can say that it's -- I very much applaud the Panel for its extensive review and its understanding of the problem. And I firmly endorse your recommendation to move this to Class II.

DR. HIRSHFELD: Thank you.

Our next presenter will be Dr. Matt Bacchetta.

DR. BACCHETTA: Hi, I'm Matt Bacchetta, the Director of Adult ECMO at Columbia University. I also am the Surgical Director of our Pulmonary Hypertension Center as well.

I'm going to just give you a very sort of boots-on-ground sense

of what's going on in ECMO today, and my two colleagues already presented a lot of very good data. This is basically how we're practicing at the University of Michigan, Kentucky, Pittsburgh, and Columbia, a volume of cases in our own institution, about 123 last year. This is what we did a long time ago, and this is what we're doing today. I don't have time to go over all of these indications and failures because of the limitation, but I'll try and touch on each of these briefly.

What are we doing in our institutions? Our typical P to F ratio is 53. A lot of comorbidities. In fact, in our own institution, 18% of those patients actually are prior transplant patients, and this is a typical configuration for ARDS, and our survival is around 74%.

There's questions about bleeding which have come up with ECMO repeatedly. Anything, even a little bit of ooze from around an IV site we consider bleeding. The clinical significance of that is significantly reduced. And as you can see in our transfusion requirements, 28 cc's per day, which is essentially phlebotomy in an ICU, is what we're using for transfusion. If you take a look at the Zapol studies and some of the others, you'll see that sometimes patients were being transfused up to a liter a day.

We looked at the use of ECMO for COPD in a pilot study, with a primary endpoint of extubation less than 72 hours. And the reason for this interest is because severe COPD patients, if they get intubated, have a 23% mortality. If they fail noninvasive and they go on to intubation, they have a

27% mortality, and there's a long-term hit for that with respect to frailty.

This basically just says that they felt better, and they felt better immediately after being placed on. The patient at the lower end of that graph was a patient that we ultimately bridged to transplant. And just a short summary of that; all the patients were extubated expeditiously. And you'll notice that the mean ambulatory distance was 300 feet. If you're taking care of patients with severe COPD, that's a pretty good walk distance. They were all discharged to home. None went to rehab, and one underwent a lung transplant and then home.

So this is what the treatment for ECMO and COPD exacerbation looks like today. This patient could not come off the vent. We put him on. The next day, he's eating lunch. And then, of course, if I can get this to work, this is what ambulatory ECMO looks like in a frail patient. It's still quite cumbersome. We've gotten a lot better with our mobilization, but it is a challenge.

So, in our short review, we've seen that it does work. Bridge to transplant, again, if you take a look at the expected survival, and you had an excellent review of ECPR, if you start comparing that with bridge to transplant for lungs, in worst case, the study that you did look at showed a 69% survival. If you take a look at our study from 2012 or the University of Kentucky data from 2013, we had 100% survival to discharge. The one-year survival at Kentucky was 93%, three-year at 80, and five-year 66%. And

basically, you're looking at a 50% survival in the UNOS database. Survival without bridge to transplant is 0%. Interstitial lung disease is terrible. It's worse than cancer. But if you take a look at how we treat patients at Columbia, if we put them on, we get 56% of those patients to transplant, 94% survive to discharge, and our current one-year survival is 91%. Without it, it's 0%. So we get 51% of the patients that we put on to transplant in one-year survival.

This is what bridge to transplant looks like in 2011. This was a patient that was failing. She was about to be delisted, pulmonary hypertension. We put her on a VA model, and she was eventually transplanted successfully and is doing well.

ECMO transport has grown significantly, especially at our center. The CESAR trial probably could have been improved if they had actually used ECMO transport. I won't go into that. We don't have time. But it is safe. This is the University of Michigan experience from over 10 years ago, our own -- we've had experience in combat casualties. Our own represents good outcomes. This is a transport I did from the San Antonio Medical Center to Columbia. Military versus civilian is very different in the resource utilization. We've had no intratransport deaths, and we've had a 67% survival.

This is what I call the extreme ECMO, when we're way out on the edge of doing things. This is from Afghanistan when I was there on a far-

forward position near the Pakistani border. This patient is being managed with a single-lumen cannula, which Dr. Zwischenberger already spoke about.

This is a young woman that we treated. She was pregnant. She had the flu, severe ARDS. We put her on ECMO, and we've delivered her on ECMO. Her baby is doing well. She is doing well. And this is not an uncommon occurrence for us. We've already had three patients like this for different reasons. Pulmonary hypertension was another reason.

So where ambulatory patients -- those of you who have taken care of patients with severe pulmonary hypertension, you know that if they get pneumonias, they usually don't do well. We don't intubate these patients anymore. We put them directly on ECMO, and then we ambulate them.

A lot of different ways of approaching ECMO. This is where we're headed, and the single lumen has made life a little bit easier for us, but we also have other --

DR. HIRSHFELD: Can you sum up, please?

DR. BACCHETTA: Sure.

DR. HIRSHFELD: Thank you.

DR. BACCHETTA: So our need for innovation is quite clear. You're addressing it now, which we certainly appreciate on the floor. And this is where we are today. What we do need to encourage, of course, is device development to extend our use. And, certainly, I think we need to look at clinical assessment of outcomes through participation and

clearinghouses such as the ELSO database.

Thank you.

DR. HIRSHFELD: Thank you.

Our final Open Public Hearing speaker is Dr. Sammy Almashat.

DR. ALMASHAT: Thank you. My name is Sammy Almashat. I'm a physician and health researcher with Public Citizen, a consumer advocacy group representing more than 300,000 members and supporters nationwide. I have no financial conflicts of interest.

In September 2013, this Panel convened to discuss the FDA's proposal to reclassify ECMO devices to Class II for two pediatric indications. The Panel agreed with the FDA's proposed reclassification. Public Citizen reiterates its opposition to the reclassification for the reasons detailed in our September 2013 testimony.

Today's testimony concerns our opposition to ECMO reclassification for acute catastrophic cardiogenic shock in adult patients for which the FDA is now suggesting a Class II designation. We urge the Panel to reject this reclassification for the following reasons:

The FDA states that a clear lack of equipoise precludes a clinical trial with anything other than a VA ECMO comparator arm in patients with acute catastrophic cardiogenic shock who would otherwise face imminent and certain death. We completely agree that such studies would be patently unethical. But these are not the only type of trial that could be required

under a PMA application with Class III designation. A non-inferiority trial comparing a newer ECMO version to an existing version would yield precisely the sort of clinical data that would guarantee that the newer device is substantially equivalent for the purposes of efficacy and safety to existing therapy. No ethical barrier of the sort identified by the FDA exists for such trials.

But regarding currently marketed devices, the absence of a single randomized trial to date leaves the question unanswered whether all currently marketed VA ECMO devices, with all the variations of combinations of technologies within the circuit, are equally safe and effective in the treatment of acute cardiogenic shock, a condition in which there is exceedingly small margin for error. How can the FDA be confident that all existing ECMO device variants, all studied in uncontrolled case series in different clinical settings with different patient populations are equally efficacious in reducing mortality and acute cardiogenic shock? Are some devices inferior or some components of some devices inferior or more likely to malfunction than others? And are patients currently dying as a result of treatment with certain inferior ECMO circuits?

Given the dire prognosis for these patients, without the best available and best functioning ECMO device, such non-inferiority trials with currently marketed devices that could be required under a PMA application would answer such critical questions or would at least go a long way to

answering such critical questions. However, grandfathering in all currently marketed ECMO circuits under a Class II designation may effectively end the prospects for such confirmatory trials.

Furthermore, the lack of sufficient information on the comparative efficacy of existing ECMO devices for acute cardiogenic shock raises serious concerns about future device approvals under the 510(k) process. And I'll refer everyone to the Institute of Medicine's report on the 510(k) process in which the Institute called for an end to the process due to its inability to distinguish between substantially equivalent and inferior new devices.

With a Class II for acute cardiogenic shock, any currently marketed ECMO device would legally qualify as a predicate device for premarket clearance of a future ECMO device without any strong evidence that it is as safe and effective as other currently marketed variants, thus perpetuating the uncertainty as to the comparative effectiveness of these devices.

The FDA's reluctance to seek further clinical trials, for example, under a premarket approval application for acute catastrophic cardiogenic shock -- and again, these would be two ECMO arms in a non-inferiority trial -- extends beyond the ethics of such trials, as it states that "anecdotal reports available and their consistency over decades of use" render unnecessary any further clinical studies, considerations of equipoise aside. We strongly

disagree. We do not believe that anecdotal reports in the form of case series or registries, which are large case series, no matter how extensive, are an adequate substitute for trials with a control arm, without which it becomes exceedingly difficult, if not impossible, to evaluate the individual contribution of an intervention to the clinical outcome. This is especially the case in critically ill patients such as those with acute cardiogenic shock in whom myriad factors and complications inevitably confound determinations of cause and effect, especially with case series.

As it happens, the FDA agrees, at least in its assessment of the evidence for the broad indication of various causes of respiratory failure for which the FDA seems to be suggesting a maintenance of Class III designation. In this case, the FDA notes that "the majority of the studies evaluating ECMO use for the respiratory failure indications for use assessed in the literature review were case series and did not include control groups. The lack of a control comparison limits the interpretability of the results as data on survival and complications related to ECMO use cannot be attributable to the actual use of the device versus to the characteristics of the patient populations who are already at high risk for death due to other complications."

Yet the FDA does not bring this reasoning to bear in its conclusions regarding the state of the evidence for acute catastrophic cardiogenic shock. Here, the FDA is content to rely on uncontrolled case

series with different patient populations, clinical settings, treatment thresholds, and of course, different ECMO device variance or component variance, in concluding that the evidence is strong enough that there is no need for further confirmatory controlled trials. The FDA thus seems to employ strikingly different standards in its evaluation of the evidence for and recommendations for regulatory classification of the two broad adult indications reviewed in its Executive Summary.

It is for these reasons that we urge the Panel to recommend that FDA maintain Class III designation with a PMA requirement for ECMO devices for all indications, including non-inferiority trials with two ECMO arms, where appropriate, for future device approvals.

Thank you for your time.

DR. HIRSHFELD: Thank you.

We now have 10 minutes for any questions that the Panel members may have for any of the public hearing speakers. I see Dr. Yuh's hand.

DR. YUH: Yes. I have a question for Dr. Lynch. You know, adult ECMO is obviously a multi-disciplinary, multi-component endeavor. With your knowledge of the ELSO data, are you seeing that the survival rates in all three categories for adult ECMO, cardiac/respiratory, and ECPR, are you seeing that the survival rates are proportional to experience amongst the different centers? Or do you have any kind of breakdown of that?

DR. LYNCH: Bill Lynch from ELSO. For the respiratory failure, yes. So we do see that there's improved survival based on experience. We're going through our data to try to also show a case per center volume mix that also is associated with experience. But, again, that number is a very hard thing to tease out. In cardiac adult support, the same. In ECPR -- I'm sorry -- in cardiac support, not the same, meaning the results seem to always be around 30 to 40% survival. In ECPR, there's not enough evidence yet to know one way or the other, but I think experience would suggest that experience is useful.

DR. HIRSHFELD: Dr. Good?

DR. GOOD: Thank you, Dr. Lynch. You talked about the ELSO registry capturing -- I think you said about 50% perhaps of the ECMO cases that are ongoing in U.S. Any thoughts about how that registry could be strengthened to include a higher percentage of cases?

DR. LYNCH: Well, the registry has gone through multiple iterations just as the ECMO technology has. So our current revision of the registry is including information to try to help us measure acuity of illness, so APACHE scores, SOFAs, other kinds of things, but then also to include manufacturers of the various devices and components that are used by each center. Unfortunately, now the ECMO ELSO registry is voluntary, and so without some strategy of having centers be required to submit data -- so for example, if it were Class II and then that were one of the special controls,

there might be an opportunity to have data coming into a very large repository where people who are experts in ECMO like the other two speakers that immediately followed me are to be able to best understand both the technology, the strategies of care, the expected outcomes that should be by patient case, and then also this question of patient center volume.

DR. HIRSHFELD: Dr. O'Connor, I think I saw your hand?

DR. O'CONNOR: So I have a question for you as well, Dr. Lynch. My name is Michael O'Connor. I'm from the University of Chicago. Is your sense that there's any participation bias in the ELSO registry? That is to say, if I were a high-performing center, I might be delighted to share my results and outcomes with the world at large, whereas if I was a center that was struggling to generate good outcomes, then we might not choose to advertise that to the world by participating in ELSO. This matters to the Panel, be it could be that the outcomes from non-registry participants might be significantly different than what you have reported, and it has kind of emerged multiple times in our conversations so far today.

DR. LYNCH: I mean, that's a very difficult question to answer. However, the ECMO community, the people that seem to be both vested in the registry as well as vested in the meetings and the organized gatherings that we have, most often, the new attendees are people who are interested in starting programs or who have recently started programs. They're

reaching out to us for guidance. So we have guidelines. For example, we have a textbook. We also offer courses. Right now, we're offering four or five courses a year, and we can't keep up with the demand. And so those participants who are interested in the learning, I think, from people who have the experience are also very interested in sharing their bad results, meaning why did this patient have a problem, what were the issues, did we pick poorly, did we manage them poorly, you know, what were the things that were related to the poor result.

So, you know, that's very anecdotal, you know. I don't know how to better describe it than that. One of things that I am somewhat concerned about is the slide that I showed showing the dramatic growth in respiratory ECMO support for adults. You know, this is growing very, very quickly. And, in part, it's growing because the technology, which is, I think, markedly safe compared to what was available for us a decade ago, is also available. And since it can't be marketed other than the distinct identified conditions for which it is now approved, industry is, I think, in some ways handcuffed to be able to offer advice and descriptions on how the technology should or shouldn't be used.

And so an example might be a new program starting, a pulmonologist that's interested. They have a cardiac surgeon and a perfusionist. And they get the technology from the operating room that might happen to be a microporous membrane oxygenator, which is great of

the operating room, but if you use it long enough, it's going to eventually fail. And unless those circle of people did not understand what technology was available, how and when it should be used, that particular program and the patients they would try to care for would be at risk.

But the inspiration to support these patients is mainly because what we're doing at the bedside, meaning ventilators, it doesn't work. I mean, these patients who are so sick and have injured lungs, they need something different. And that's why I think there is becoming this sort of ground swelling of interest in ECMO from the lay physician.

DR. HIRSHFELD: Okay. Thank you.

I'd like to inquire whether any of our Patient, Consumer, or Industry Representatives have any questions or comments they'd like to make?

Yes?

MR. THURAMALLA: I'm Naveen Thuramalla. I'm the Industry Representative. Among the centers that report to the ELSO registry, what would be the proportion of U.S. centers versus rest of the world?

DR. LYNCH: So it's -- again, I'm going to guess. It's probably 80% or so U.S. centers. That is changing, though. We now have sister organizations in Europe, in Asia, in South America, and so the worldwide interest in ECMO unrelated to ELSO is growing in a similar way as it is in the United States. But the fact that now we have other internationals that are

contributing data to our registry, I think, gives us power to better make sense of what's going on both throughout the world, but then, also, better strategies in managing these patients safely. So, again, our registry I think probably is suggesting 80% of what we have in our database is from United States centers.

DR. HIRSHFELD: Dr. Zuckerman, did you have a question or a comment?

DR. ZUCKERMAN: Dr. Lynch, thank you for coming to this meeting. You're substantially helping us out with your comments, and I believe that Dr. Laschinger from FDA had a question for you.

DR. LASCHINGER: Yeah, thank you. John Laschinger, FDA. I just had the one question to touch on the experience factor you talked about. And you suggested from the ELSO registry data that with increased experience, results get better at centers, although overall, for at least ECPR, if you look at the overall data, with increased experience over the recent years, actually the mortality has gone down possibly due to more aggressive use and inappropriate, you know, or borderline situations.

But for the experienced centers themselves, do you think that their results are getting better because of, you know, selection bias, knowing who to select better and also because maybe select patients earlier than might be -- or more aggressively than might be done in some centers where they wait till the patient is further along on a course, and what effect do

those things have on mortality?

DR. LYNCH: So I'll try to remember your questions, but remind me if I forget. The idea of experienced centers and improved outcomes was that was your question? The evidence for the ECPR is very hard to interpret, I mean, for all patient cases. It is clear, though, that when you are choosing your patients, there are certain patients that seem to best benefit from being supported by ECMO and others that don't seem to have the same results. So, as an example, in adult respiratory failure, most of the evidence suggests that if you put a patient on adult ECMO VV support for respiratory failure who's been on a ventilator for longer than seven or eight days with traumatic ventilation settings, then their results are equivalent whether you put them on or you don't put them on. If you put that patient on day two, day three, then the results seem to be better, both survival and discharge survival. And then the argument is, well, did I put somebody on that didn't need it, or did I just pick appropriately, and that's very, very hard to say.

The fact that the technology is safer allows us to sort of make a mistake in the wrong direction, meaning put somebody on that maybe ultimately didn't need it, but knowing that the chances of you hurting them with the technology and the strategies of support are very low, and if you can give that patient a benefit, get them off a ventilator, get them off sedation, then the advantages might be very high.

The second question you had, remind me, was -- oh, okay.

DR. HIRSHFELD: Okay. Yes?

DR. ZEHR: Kenton Zehr from Baltimore. I'm wondering who funds ELSO, and are there plans in the future for auditing data that gets sent in, say, in a more robust way like the Society for Thoracic Surgeons' database?

DR. LYNCH: So ELSO is a voluntary, nonprofit organization. The funding for ELSO comes from member centers who pay a fee each year, and so that's from the hospital. The data that we have is self-audited by centers. We are trying to put a mechanism in place where we selectively choose programs, go there and try to audit their data. But, again, we are limited by the fact that we're a group of volunteers, and it's hard for us -- just like you to be here, it's hard for us to go from center to center and query their data. I think to best defend and protect the integrity of our data, that will be necessary in the future.

We do have a mechanism through our organization to identify centers of excellence, and that is a very lengthy, involved process, but part of it has to do with the education and training of specialists, the number of cases they do, the survival outcomes that they have, and how it compares to our registry. And so the value in centers being an ELSO member representative is if you're starting a new program and you want to see how you're doing, then you have something to reference, and that data is shared from our organization to each of the member centers.

And for that matter, the data is available to others for important purposes. So we're working with the national government in England. They're providing a study to try to look at ECMO in the setting of COPD and clearing CO_2. And we have made our registry available to them, and that same offer would stand for this Panel if that were to be of benefit.

DR. HIRSHFELD: Thank you.

Dr. Yuh, you have a question?

DR. YUH: I have a quick question for Dr. Bacchetta, just from, you know, a high-volume ECMO center. And this speaks towards the risk profile for adult ECMO. Are you seeing with the extended periods of time that adults are being placed on ECMO, whether it be veno-venous or VA, higher incidences of HIT? Are you seeing that in your patient population?

DR. BACCHETTA: Matthew Bacchetta from Columbia University. No, actually, we're not. A HIT is a very rare complication that we see. It's certainly no more than the literature, and even with our long-term support, we don't see an increasing incidence of that.

DR. HIRSHFELD: All right. We are exactly on schedule. It's 10:25. We're now scheduled for a 15-minute break. So we will restart again exactly on schedule at 10:40.

(Off the record.)

(On the record.)

DR. HIRSHFELD: Welcome back. And we're now going to begin

the Panel deliberations. And this portion of the meeting is open to public observers, but it's not open to participation by public attendees unless there's a request to ask something of one of the public attendees. And as usual, we would like everybody to make sure that they identify themselves.

So my first question is does anybody on the Panel have something -- a question that they would like directly to one of the FDA presenters for further clarification on their presentations?

Dr. Kandzari?

DR. KANDZARI: Thank you. Good morning, again. This is directed for Catherine Wentz's presentation. Good morning, Catherine, and thank you. I have two unrelated questions for you. One is that you had presented some data regarding over the past, roughly, decade, three recalls related to the device technology. And I was curious if you could provide further information regarding those recalls.

And, secondly, in I think December -- or excuse me -- January 2013, there's a proposal by FDA, and it's summarized in the Executive Summary, with regard to moving away from the anesthesiology requirements, changing some of the nomenclature of ECMO as well.

And the third component is this issue of 6 versus 24 hours and the timing of duration of support. And I'm confused by that now. Is it 6 hours, 24 hours, what we're talking about, and does that have any relevance with regard to reclassification?

MS. WENTZ: Thank you, Dr. Kandzari. This is Catherine Wentz.

So to answer your first question about the recalls, there were three recalls over the 11 years. The first one was for an oxygenator, the other two were for cannulas, the specifics of which I do not have. But usually, it's a severe device malfunction, cannula breaks, oxygenator tears, something like that. But, again, only three in the 11 years. And once again, we don't know whether that was an ECMO procedure or a bypass procedure.

Regarding the change from the anesthesiology panel to the cardiovascular panel, it has been and currently is in the anesthesiology panel because it's an oxygenator. That makes sense. ECMO, however, is the exact same thing as a cardiopulmonary bypass circuit, which is all reviewed in cardiovascular. So even though the devices are currently under the anesthesiology regulation, we have always reviewed them because we have the expertise, both the clinical and the engineering expertise, to review those devices. So we just figured let's -- while we're going through the reclassification, let's pull them back out of anesthesiology and bring them into the cardiovascular panel.

Regarding the 6 versus 24 hours, this came up at the pediatric one as well. Again, since we are having this reclassification effort, let's, you know, tie up all these loose ends. Six hours of use and less has been the duration of use for bypass devices. The current regulation for ECMO is 24 hours or greater. So what happens to those devices between 6 and 24

hours? That's a big question. Would that be a short-term use or would that be long-term use? So what we've decided to do is close that gap. And ECMO would then be considered anything behind normal cardiopulmonary bypass use, so beyond six hours.

DR. HIRSHFELD: Yes?

DR. ALLEN: So, Catherine, that segues into my next question, then. How does the FDA -- so, for example, you take a generic cone or a centrifugal pump off the shelf that's approved for bypass, and you cut it into an ECMO circuit, and now you're going to use that cone instead of six hours, for what it may be approved for, now you may have some -- put somebody on VV ECMO with that cone for 25 days. How is the FDA going to develop equipoise between devices that are currently approved but then can be cobbled into these circuits? Because as it is, it's very much institutional unless you buy a pre-specified, you know, MAQUET-type mobile product. Most places, as we do, have our own set of circuit system pumps that we put together that we think work the best. But they may not all be approved for the right lengths of time and so forth. So how are we going to manage that?

MS. WENTZ: Right. Again, this is Catherine. So you're kind of meshing practice of medicine with this reclassification process. So the reclassification process, whether it be Class III or Class II, is going to determine what that device label is going to be able to say. So, for example, if we have a centrifugal pump, and we decide on Class III for respiratory, and

they want that label, they're going to have to show us that that device can be used for 25 days or longer. They have to show us through bench testing, through animal testing, through clinical testing. It will be labeled that way. If we're going to go Class II, depending on whatever duration of use they want -- maybe it's only going to be the two or three days, you know, that we talked about before -- then all they'll have to do is show us whatever duration of use on their label.

DR. HIRSHFELD: Okay. Let me just pursue that for a moment, because I'd like to get absolute clarity on this. So we've been led to understand that FDA is now recognizing the entire circuit more or less as a -- although it says multiple components that they're considering that to be a unit. So from a regulatory standpoint, is there going to be a requirement of certification of compatibility of individual components with each other? And will there be particularly approved combinations of components manufactured by different manufacturers that will need to be independently certified as being compatible?

MS. WENTZ: Excellent question. Again, this is Catherine Wentz.

So we understand that all of the different components usually come from 10 different manufacturers. So we can't require the manufacturers to make a circuit. And so we wanted to build into the regulation some flexibility that will allow us to regulate and review individual

devices, yet be determined safe and effective for ECMO therapy.

So, for example, each of the components of the circuit, if it were to be reclassified into special controls, each of the components in the circuit would have its own set of special controls that it would have to meet in order to be determined as safe and effective. That could include duration of use on the bench and with clinical data. It would include compatibility. That would be included as part of the labeling and performance standards. It would include biocompatibility. It would include that list of, you know, general special controls that you saw earlier as well, as well as the very specific performance-type standards for each of the components.

DR. ALLEN: And I appreciate that explanation. And you're right. I do, as a clinician on the Panel, I'm always trying to weigh, you know, what the FDA's mission is, what as a practicing clinician I might do. But let me be even blunter, because let me just be where I'm thinking very nefariously how a company could use this reclassification as a faster, more rapid, less expensive way to get a product to market, which then the FDA approves it for -- under a Class II indication for ECMO, but that's not really then how that device is used. And it's used in other ways per the purview of the physician. And I realize that's not the FDA's role. But it does open some -- perhaps some confusion or loopholes that could be exploited. And I just want to make sure that -- and I know the FDA has thought about that and how they might handle that, or perhaps it's not in your purview. Perhaps

that is -- it's just medicine has to take care of that outside the FDA?

MS. WENTZ: No, that's an excellent concern. It's definitely something that we've thought about. So let's give a concrete example. Say we go with a split classification today, and some indications we go with Class II, and some indications we go with Class III. I think what you're saying is these manufacturers are going to go that fast route to Class II and know that it's going to be used for the Class III anyway. And what assurance do you have of the safety and effectiveness of that device to be used in the Class III indications? Do I have you spot-on?

DR. ALLEN: Spot.

MS. WENTZ: Okay. So what the FDA has -- the mechanisms that FDA has to address this is if in the Class II arena these devices will be labeled, marketed, and promoted for those Class II indications. And that will be their limit. If we find that they are labeling, promoting, or marketing for the Class III, our Office of Compliance can then step in. Practice of medicine, however, will not be affected. So if the physicians feel that they need those devices in order to treat the patients in these Class III indications, that is fine. We will not limit -- we do not get involved in the practice of medicine.

Have I answered your question?

DR. ALLEN: Yes, you have.

DR. HIRSHFELD: Okay. Other questions in this generic area?

Yeah, Dr. O'Connor?

DR. O'CONNOR: I had a question as well. You know, I also was interested in the recall rates. So we talked about the Class I recalls, of which there were three, and then the Class II, there were many. Because we're not with the FDA, we don't know how that compares to comparable devices, and that matters as we think about the safety of these devices. I mean, on your slide 22, you have 156 Class II recalls, and you have 17 which are the Class III recalls, which are the less important ones. But I mean, is that a high rate? I mean, is this the kind of thing where these represent significant hazards to patients?

MS. WENTZ: Okay. This is not my area of expertise, so somebody may want to step in for me, but just for, in general, a Class I recall is usually when a death, you know, or deaths have occurred. So those would be major. Class II is injury and Class III is very minimal. So put that in perspective. And I can't remember the second part of your question.

DR. O'CONNOR: Well, we're charged with thinking about the risks and benefits of these devices and the reclassification scheme. So for myself, I mean, 156 Class II recalls, I mean, how does that compare to comparable technology that the FDA evaluates?

MS. WENTZ: So how does that relate to how many of these devices we see and use on a daily basis?

DR. O'CONNOR: For comparable devices that the FDA has reclassified.

DR. ZUCKERMAN: Okay. I think that's a great question, but it's a little bit difficult to answer for the following reasons. You know, to answer that, we would have to know the other devices that you're referring to, and we would have to get a better assessment of denominators, et cetera, so we can just provide a gestalt at this point. One is that, you know, as Catherine mentioned, the number of Class I recalls, which are very significant, has fortunately only been three over a decade of experience. So our general impression, it's not an exact impression, for sure, is that this has been a device category that has not caused an excessive number of problems where we think that we may not be evaluating these devices correctly on a preclinical engineering perspective such that we're missing major issues.

Catherine, do you want to elaborate on that point?

MS. WENTZ: I think the only additional point I'd like to make -- you know, Bram is exactly right. But you also have to bear in mind that ECMO is watched very closely and very carefully. And whenever someone notices that there's something going wrong with a device, it'll get switched out. So we don't get a lot of the problems reported because of the great oversight in ECMO.

DR. HIRSHFELD: I'd like to propose that with our remaining time that we organize it in part -- we had a great deal of discussion about the efficacy and the indications for ECMO both in the cardiac arena and the pulmonary arena. So I think since a lot of what we're going to be discussing is

our concepts of how we feel about the appropriateness and the indications of these techniques, I think I'd like us to spend -- focus our discussions for the next several minutes, at least, first on the cardiopulmonary indications, and if anyone has questions about that, and then we'll go to the pulmonary indications after that.

So does any Panel members have any questions about the cardiopulmonary efficacy and indications for this?

Dr. Lange?

Okay. Yes, Dr. D'Agostino?

DR. D'AGOSTINO: I'd just like some clarity with all of the items in front of us, actually. The data was very nicely reviewed, and it's not very substantial in terms of clarifying effectiveness, as was stated. It was done very well. If we recommend switching, is that going to -- and I'm not sure of all the implications, but is that going to really accelerate the problem with not having data to endorse these -- to substantially endorse this? If we stay Class III, there's certain rituals that one has to go through, and if we move to a different class, it's less so. And, you know, one of the public speakers was talking about these non-inferiority tests. I'm not sure how that all plays out, but doesn't -- I don't see the level of rigor being maintained if we switch, and could you give some implications on -- well, what are the implications of the switch in terms of these items?

DR. LASCHINGER: John Laschinger, I'm going to give you the

clinical perspective, and then Catherine will give you the regulatory perspective.

I think as opposed to respiratory, with cardiac causes for ECMO, there -- you get to a point where there are no other options and you have to institute ECMO or declare the patient, you know? So at that point in time, there is really no equipoise for therapy because of the sudden onset and the acute onset. And so to generate sufficient evidence for demonstrating safety and effectiveness in that situation is going to be almost impossible, because really the alternative is zero.

Now, in the pulmonary indications, it's much different. As you heard --

DR. D'AGOSTINO: My question was sort of general, but I wanted the distinctions as you're making them. Thank you very much.

DR. LASCHINGER: Yeah, okay. But in the pulmonary indications, as the doctor from the ELSO registry talked about from the University of Michigan, it's, you know, whether you institute it at two days or seven days gives you a whole range of time there where does it work at -- you know, if you institute it at two days and have some patients where you don't institute it at two days, what are the differential outcomes here? We don't have sufficient evidence to know that effectiveness if you do it at three days or five days or immediately, because the patients at that point in time aren't immediately facing death without ECMO. They're facing continued

deterioration possibly and maybe, you know, progressive lung injury, but we don't know where that line lies, and we don't know how to determine what's safe and effective in those patients and when it's needed or not. I think that's the major distinction between the two.

MS. WENTZ: And then just to add on the regulatory definition, which I think may address your more general question, is that in order to down-classify something, you've got to have enough valid scientific evidence to assure the safety and effectiveness of that device for those indications in order to reclassify it to Class II. So you have to be pretty sure that the data that's out there, the valid scientific data that's out there, is enough to assure safety and effectiveness for those indications. Otherwise, it will remain in Class III.

DR. HIRSHFELD: Okay. Well, Catherine, thank you for that clarification.

So are there Panel members who have further questions about the clinical evidence for cardiopulmonary ECMO?

Dr. Lange?

DR. LANGE: Let me just get some clarification with the FDA. When you say cardiopulmonary, that could be a cardiac issue or a pulmonary issue. We're talking -- I want to make sure that we're talking about an indication for acute cardiac decompensation. Is that fair?

DR. HIRSHFELD: Yeah, that was what I had in mind also --

DR. LASCHINGER: Yes, for Class II, yeah.

DR. HIRSHFELD: The terminology in a lot of the documents says cardiopulmonary, but the primary issue is --

DR. LASCHINGER: Right.

DR. HIRSHFELD: -- cardiac?

DR. LASCHINGER: Yeah, and that's why -- John Laschinger again -- that's why I tried to make the distinction based on the causative, the underlying cause based on acute, you know, catastrophic cardiogenic shock. And that's how we look at the cardiac causes, yes. And then there's the primary pulmonary etiologies was the second classification.

DR. LANGE: And the reason I bring it up is, again, if we're going to make a Class II, Class III distinction, if the Class II says cardiopulmonary, it may be interpreted as including pulmonary issues like cardiorenal would include renal issues. So just you may want to clarify that.

DR. HIRSHFELD: Yes, Dr. Allen?

DR. ALLEN: Catherine, I think probably you could answer this the best. You know, all of the individual components that go into ECMO, they've either been reclassified -- so, for example, centrifugal pumps have been reclassified to Class II; tubing is Class I or Class II; cannulas are Class II. All of the individual components that have already -- are already Class II, what you're really asking us, then, is when you cobble them together as an ECMO circuit, can that be classified as Class II. So everything we currently are

looking at is Class II. You're just looking for the ability to label something for ECMO that then would be a reclassification. Is that correct? There's not anything now that is Class III -- technically, I guess --

MS. WENTZ: Technically, there is still one that is Class III, but -- so I think what you're saying is that can you have a device that's Class III -- so I think what you're saying is that can you have a device that's Class II, on the market Class II, and have it on the market as Class III for a different indication, and yes, you can. You can have the same device on the market for two different indications being two different classes.

DR. ALLEN: I guess what I'm -- I guess my point is for the Panel is that all of these individual components of ECMO have been thoroughly vetted by the FDA or previous panels and really stand as Class II devices --

MS. WENTZ: For bypass.

DR. ALLEN: For bypass. And what you're asking now is can we extend that to ECMO, which, quite honestly, is just bypass.

MS. WENTZ: Prolonged bypass, right.

DR. HIRSHFELD: Yes, Dr. Zehr?

DR. ZEHR: Kenton Zehr from Baltimore. But correct me if I'm wrong, there's no polymethylpentene membrane which has been approved for nearly as long as what we're using them for. So say, for example, my personal clinical experience, my longest successful ECMO was 78 days. Now, we well know that certain pump heads will crush a patient in 78 days if

they're utilized in that -- you know, for that indication. Switching them out just doesn't help. You're going to have hemolysis, renal failure, and the patient won't survive that long with that component. So there are definitely components that can be used in different ranges. So I'm wondering if we -- you know, if we make this Class II for all of these components, you can have anything from a cone that costs $350 to, you know, a Mag-Lev head which costs 15,000, which may get your patient out with the same head out to 78 days. So I'm wondering how we're going to vet these devices as they come in.

MS. WENTZ: Good question. So as we tried to cover before, each of these devices will have their own set of special controls if we go reclassification. They will have their own set of special controls, which will include clinical data in the very broad category of in vivo data, which was one of the broad categories of special controls that was suggested. So each one of these devices would have to come in with clinical data showing that they are safe and effective in whatever the indications we have reclassified, cardiopulmonary, ECPR. They've got to show that they are safe and effective for whatever duration of use is indicated, and that will be in their label.

So if we've got the Levitronix one that has been able to demonstrate through clinical study that can be used for 45 days, that'll go in their label. If the other cone pumps can only show that they can be safe and effective out to seven days, that's what's going to go in their label. Does that

answer your question?

DR. ZEHR: Yeah. It's a huge leap forward considering what our indications for temporal use is now. I mean, what's the longest approval we have now for a pump head?

MS. WENTZ: So there have been no centrifugal pumps to my knowledge that have been cleared for ECMO.

DR. ZEHR: That's why I'm asking the question.

MS. WENTZ: Yes. And they will have to come in with clinical data as well as duration, you know, duration of use or liability, durability data on the bench in order to, you know, show their safety and effectiveness for marketing.

DR. ZEHR: And even a Quadrox D oxygenator is approved for how long?

MS. WENTZ: Six hours.

DR. ZEHR: Not 78 days?

MS. WENTZ: No.

(Laughter.)

DR. ZUCKERMAN: Right. But, Dr. Zehr, what percent, approximately, of your ECMO cases are above, say, 50 days?

DR. ZEHR: In a series of 100, the average ECMO run is 16 days.

DR. ZUCKERMAN: Right. So, you know, the FDA, in regulating devices, takes into account usual practice, what a firm wants on the label,

and you know, as Catherine has indicated, I doubt the first time through companies would test on a clinical basis that long as opposed to something shorter, where we would label it, and then if you felt compelled for a certain case that that's the best treatment option, it would be practice of medicine.

DR. HIRSHFELD: Dr. Zuckerman, could maybe I try to restate this a little bit to try to achieve clarity on this issue? So we are talking about devices which currently have approved labeled indications for cardiopulmonary bypass, all of the various components of the device. What we're asking today is how do we extend the use of those devices to ECMO, and does that constitute -- these are devices which are approved, they're marketed, they're labeled for cardiopulmonary bypass. Now I think the Agency is asking we now need to confront the issue of the use of these same component devices for long-term either veno-venous or veno-arterial support not just to do a cardiac operation, but for other purposes. And that's the issue that we need to distinguish.

So in response to Dr. Allen's question, they're all on the shelf. They can be cobbled together into a circuit. But it's for a different purpose, and it's the purpose that we're addressing at the moment. Is that a fair summary?

DR. ZUCKERMAN: Okay. Why don't we let Dr. Allen respond first, and then I'll respond.

DR. ALLEN: So I love it when my light bulb goes on, because

when I was listening to Catherine just a minute ago, she really hit the nail on the head. Actually, reclassification of devices, in my mind, may actually make this whole process safer and simpler, because right now, it's the Wild West. You cobble together devices. Very few of them are labeled for how you're using them. And it is very prohibitive for companies because there are so many different devices that go into the ECMO circuit, no one company can pull all that stuff together and do a trial to get under the Class III bureaucracy.

But what now you have is you've got a product that is approved for cardiopulmonary bypass. And what Catherine said is the company, then, will need to come in and demonstrate through special controls that the FDA will set up that it does meet requirements for a Class II indication for ECMO. And now you can have companies that actually will make the effort to come to the FDA to get labeling that's appropriate for how it's being used clinically because they can afford to do it and can -- is that kind of what you said?

MS. WENTZ: 95%. Can I just clarify one thing?

DR. ALLEN: Sure.

MS. WENTZ: So we've been talking about special controls and reclassifying and how would we get those devices on the market. If there's not enough safety and effectiveness data on the market for an indication and we believe it's Class III, it will go through a similar process of requiring clinical

data to show that clinical endpoint and to show that that device is safe and effective just in the PMA arena, okay? So you need to always bear in mind that we have to have enough valid scientific evidence to assure safety and effectiveness in the certain indication. And then once we can parse that out into Class II and Class III, then we worry about -- gotcha, okay.

DR. HIRSHFELD: Okay. Let me go back to Dr. Zuckerman to take us a little farther down the clarity road in this issue.

DR. ZUCKERMAN: But I think that the discussion over the last few minutes has been very helpful. And to keep it simple, I think that Dr. Allen's comments are very helpful. The reality right now is, for a variety of reasons, firms have the ability to do an end-around, or as Dr. Allen described it, it's the Wild West. Now, this has been going on for a while so that there's going to be no perfect fix. But certainly having a better idea of how these devices operate in potential systems with appropriate labeling can serve the public health's interest, and that's where the FDA is coming from with these proposals today.

DR. HIRSHFELD: Yes, Dr. D'Agostino?

DR. D'AGOSTINO: And trying to follow it, and I really find Dr. Allen's ideas very exciting. The trouble I am having, if I maybe don't understand the classification, what is the data that's sitting there now that would say there's enough to move it into a Class II so that then the things that I think you're talking about can happen?

DR. ZUCKERMAN: So, Dr. D'Agostino, let me give you and some other Panel members context, because the idea of data spelled with a capital D is very challenging in this area. And as you heard, the Panel the first time through thought that perhaps we should only be considering this template in the pediatric arena. But experienced clinicians on this Panel who were at the first panel like Drs. Lange and Cigarroa felt that from a clinical viewpoint, as opposed to a rigorous clinical and statistical viewpoint, we should at least have this discussion regarding the merits of the adult data. It'll be a tough discussion for this Panel. And, you know, I think we have excellent Panel representatives, and that's why Dr. Hirshfeld wanted to get us to start this discussion, because that's the crux of the matter.

I mean, when we look at the data from a combined clinical and statistical perspective, I think -- and I don't want to put words in anyone's mouth -- things are lacking. And we have to be careful. But because at the first Panel meeting there was a real interest to have this discussion, this is why we're here today.

Dr. Lange, do you want to give us some more context so we can start this clinical discussion?

DR. LANGE: I think that summary is excellent, because when we looked at the data in September, there was -- we looked at all the pediatric and neonatal data and very little of the adult data. And that was partially a reflection of the MeSH terms that were used to obtain the

information. And at that time, we asked to come back and say let's look at the totality of the data, limit it to adults, and see whether there is compelling evidence to reclassify it either for cardiac issues or for pulmonary issues.

DR. D'AGOSTINO: This is exactly the type of response I was looking for. Thank you.

DR. LANGE: Yeah.

DR. HIRSHFELD: Yeah, Dr. Brindis?

DR. BRINDIS: Just building on this discussion, I'm interested in feedback. Is one way of looking at this, if we decide on a Class III, then we have to go back to PMA, we have to ensure that we have a safe and effective system. If we move it to Class II, we can put in all sorts of, you know, special oversights to at least we can ensure that it's safe. And the efficacy issue we may be able to look at possibly through beefed up registry oversight or something of that sort, but at a different level. Is that a fair comment?

DR. ZUCKERMAN: Okay. Dr. Brindis, I think what you're saying is that, certainly, if for this class of devices for a specific indication, a recommendation is made by the Panel for Class II, we have a variety of ways through both preclinical data evaluation and also clinical data evaluation for particular components to assure us that we have reasonable safety and the devices operate within reasonable parameters when they're used as a system.

Catherine, would you like to add anything?

MS. WENTZ: So what I heard you saying is that as long as you think the device is safe, then you can put it into Class II. And what Bram said, we have to have a reasonable assurance of safety and effectiveness based on the data discussed today for those indications that are being recommended for reclassification.

DR. HIRSHFELD: Okay. Dr. Cassiere?

DR. CASSIERE: I'd just like to voice my opinion that, at least looking at the data, the cardiac indications support a Class II with restrictions. I have reservations about moving it from -- out of a Class III for the pulmonary indications. I think there needs to be a lot more robust data on the pulmonary indications. One of my concerns, if we reclassify it in Class II with restrictions, the use of it in the pulmonary population is going to go even higher than the tenfold. It'll be a hundredfold. And if we don't have control on the companies and their marketing, which is very difficult, these devices will be used on everyone with a COPD exacerbation, cystic fibrosis patients. I can go down the list of things that this would be used for.

DR. HIRSHFELD: Thank you. And we're going to return to that when we actually get to the FDA Panel Questions.

Dr. Cigarroa?

DR. CIGARROA: Thank you. It's interesting. I share similar concerns. I think that as we evaluate the totality of the data, coming back and having FDA redefine demonstration of efficacy with regards to data, I

mean, it's interesting. The data sources do not need to be randomized controlled datasets, and there's an extensive list that falls under the totality of the evidence.

With regards to safety, obviously, what is the reference point? And, you know, these are complicated systems. And I think the reference of what is tolerable depends upon what the patient's natural history is going to be. And then again, you know, what is the probability that you can improve it in a positive direction? And so we must understand looking at the totality of this dataset, the referral biases that are present in the ELSO registry. It's voluntary. We have heard from the head of that registry that, A, it's voluntary; B, that there may be at least only a capture of 50% of the patients that are actually receiving these therapies; and, three, there are no formal audits like we are used to seeing in other datasets. And so I'd simply come back and say let's go over what those definitions are before we enter our formal addressing of the individual questions.

DR. HIRSHFELD: Dr. Kandzari?

DR. KANDZARI: Just as a follow-up on that comment, though, I think that a well-designed special controls registry could provide probably more valuable information in this setting than 90% of the existing clinical trial that's available to date. Notably, most of this data has been generated from either single centers or multicenter experiences, but it's been largely investigated or initiated.

I wanted to get a comment more from Bram and Catherine, though, just to clarify FDA's position about the emphasis on assurances of safety and efficacy and the available data that we have to date with all the limitations that have already been mentioned is that what -- wouldn't you also agree that there is the element of experience, too, that needs -- that this Panel needs to consider, experience with this technology, these devices in other clinical settings as well? And I say that based on the 23-25 years of experience with extracorporeal membrane oxygenation that we have already. And it reminds me of our classification meeting regarding intra-aortic balloon pumps. There's a lot more data with intra-aortic balloon pumps, but you know, the data is not exactly compelling regarding their safety and effectiveness as well. But the classification was motivated largely based on the experience with balloon pumps. And I remember that was something that I think you in particular had referenced oftentimes as well.

And so I just wanted to get a comment from you because I know we're going to focus on the limitations of the data so much, but you would also consider -- FDA would consider the experience as well? Is that fair?

MS. WENTZ: So I'll let Bram take this after me, but I'll take a stab at it. You're right. We are going to be considering both. And in the case of intra-aortic balloon pumps, if you remember, the reclassification was for a subset of patients that we felt we also had enough safety and effectiveness

to include it along with the experience in order to reclassify. Anything that fell outside of that remained in Class III.

Bram?

DR. ZUCKERMAN: So, yes, we would recommend that you try to utilize your complete knowledge base and to try to leverage other experiences to the extent possible where it makes sense. And that's both from a preclinical and clinical perspective. But for the purposes of this Panel discussion, it'll probably be in the clinical sphere, but it's a good point that you're making, Dr. Kandzari. And if you can use the same principles you used at the balloon pump meeting, that would be helpful to help this Panel.

DR. HIRSHFELD: Yes, Dr. Jonas?

DR. JONAS: Yeah. I have a question regarding the practicality of designating an entire circuit as a Class III device. I mean, there are so many permutations in terms of the different components that I think we need to clarify -- are we talking about classifying individual components like a Quadrox oxygenator or a centrifugal pump head, or are we talking about an entire circuit? Because I would submit that classifying an entire circuit as a Class III device and expecting randomized trials to be conducted of a circuit is just impractical.

MS. WENTZ: So we have a precedent hemodialysis circuit. It falls under one regulation as well. So we would kind of follow in that same step, where we would define the circuit in the regulation but identify that it is

composed of many different components. So each of the components will be able to be reviewed under that one regulation but be reviewed separately and on its own merit.

Does that answer your question?

DR. JONAS: And it's been classified as a Class III device?

MS. WENTZ: If that's what the Panel recommends and what FDA ultimately decides, we can put all of that into Class III.

DR. JONAS: No, but I'm asking has the hemodialysis circuit been classified as Class III?

MS. WENTZ: No, I think that's a Class II.

DR. JONAS: That's my point --

DR. ZUCKERMAN: Now it's a Class II, but --

MS. WENTZ: Right.

DR. ZUCKERMAN: But, you know, again, I've been really impressed with this Panel. I'd like to hire all of you as FDA regulators because you're interested in both the clinical aspects and how we practically put it into a regulatory context. But I would like to get back to Dr. Hirshfeld's challenge for all of us.

The first thing is we need from you a better understanding of the data. For example, I want to thank Dr. Cassiere. He indicated that he wasn't persuaded with the safety and effectiveness the so-called pulmonary indication even though there's widespread growth in the United States.

What would be helpful for the FDA is to hear from other Panel members as to how they interpret both the published data and some of the speakers' presentations that they heard today.

And perhaps, Dr. Nathan, you can help us here?

DR. NATHAN: Yes. I've been listening with great interest to some of the comments. And just a couple of things. First, I think the practicality of having it as a Class II device and a Class III device for different indications, I'm not sure if that's going to lead to confusion or if it's going to raise any issues and if it's going to make a difference clinically. And just to the point that you made earlier, in terms of people rushing out to put CF patients and COPD patients on this device or using this technology if it's a Class II versus a Class III, I don't think that's the barrier at all to implementing this. I mean, there are many other barriers to using ECMO in terms of being resource-intensive, et cetera, et cetera. I think if there was going to be a rush to do this, it would have happened already. I think probably many folks in the field, many clinicians don't even know the difference between a Class II and a Class III device.

I think if you think about doing studies with this, and you think about the design of studies, it's always good to have data, and we should try and accumulate data, but just thinking to the design and the nitty-gritty of a study, I'm not sure if it's feasible in some ways. I'm not sure if it's ethical. If you think about the patient population that I deal with a lot, and that's the

lung transplant patient, how do you sell this, how do you sell a study to a patient like this? Do you say to them I don't know what the comparison is going to be? We can put you on this device. You can be walking; you can be eating. We can keep you going for two weeks, three weeks, four weeks until we get a donor for you. I'm talking about a patient who has advanced cystic fibrosis or pulmonary fibrosis. Or we can put you on a ventilator. We're going to have to sedate you, paralyze you perhaps, and you might last a week or two before -- and that's the window you're going to have before you're eligible or not eligible for a transplant. So in terms of the feasibility of doing a study like this, I'm not sure.

And then you look at the patients who are -- you look at the concept of ambulatory ECMO and the fact that patients can walk around and maintain their strength. And so what do you compare that to, in terms of what's the other group you're going to do a non-inferiority study to?

So I think we'd all like to see data, but sometimes, the technology leapfrogs so far forward that to do a study that we can hang our hats on becomes quite difficult.

DR. HIRSHFELD: Yes, Dr. Cassiere?

DR. CASSIERE: Yeah, just to follow up. My comments had nothing to do with exact patient care. It's company marketing. So if MAQUET wants to come into my institution and say use this device, I'm going to push you to use this device on the COPD patients and cystic fibrosis

patients, they should have data to back that up. We should not give them a ticket to come into our hospitals and say you should be using this on patients when there's no indication. Granted, if you have a COPD patient and they're in dire straits, and you want to do AV ECMO or VV ECMO, so be it. But we should not be giving the companies a free pass when there's no data.

DR. ZUCKERMAN: That's well stated, Dr. Cassiere, as to how our regulatory system should ideally operate. And can we ask you to take it one step further. You heard a lot of discussion from the FDA team this morning regarding the ARDS population and perhaps some major questions about interpretation of the one randomized trial, the so-called CESAR trial. Can you help us understand how you look at that patient population? What do you make of the CESAR trial? What do you think is standard of care?

DR. CASSIERE: Well, I think it was interesting that when you referred a patient for ECMO, 14 or 15% of those patients did not receive ECMO. They were sent to centers of excellence. And I'm pretty sure those patients were proned or some other therapy, or by the time they got to the center, they had improved ARDS so they did not need the ECMO. So in my mind, there's still -- you still need some stringent data to show that ECMO is efficacious versus proning, even the use of nitric oxide. We should have the same standard for if I'm going to use nitric oxide on a patient, which I do with ARDS, that's not FDA-approved. We should have the same standard for ECMO. It is a therapy. It is a supporting therapy, but when you're using it for

that indication, it is a therapy.

DR. HIRSHFELD: Related to that, we haven't heard anything from Mr. Branson today. Sounds to me like this is in your wheelhouse.

MR. BRANSON: So I was going to say when I look at the risk/benefit, the issues has to do with reversibility of disease. So when you look at a patient with severe ARDS who, absent VV ECMO, the mortality is very high, the duration of mechanical ventilation is high, delirium, frailty, long-term costs, to me, there it makes sense that VV ECMO or whatever your version of ECMO is a Class II device.

My concern is the same. How do we determine reversibility? There are lots of COPD patients. Is it an acute exacerbation of COPD that qualifies for ECMO, or is it everybody who qualifies for ECMO? And then you run into the ethical dilemma of what happens when their lung disease isn't reversible and you have to take them off of ECMO even though they're walking with ECMO and they would expire without it. Well --

DR. HIRSHFELD: Dr. O'Connor?

DR. O'CONNOR: Right. Michael O'Connor. So a couple of observations. I think that regardless of what the FDA makes as a decision here, I think that you should ask the manufacturers to certify the components for something more than six hours for use in general so that regardless of how we classify them at the end of the day, I think some reasonable duration of use, 16 days, 32 days was the earlier stipulation, I think that should happen

regardless of what the Panel does.

You know, for myself, a randomized controlled trial of ECMO in cardiac arrest is like a randomized controlled trial of parachutes, right? It's not possible. What you need to do is you need to just kind of look at what the outcomes are of what it is that you do.

The respiratory indications are a lot murkier for me for several reasons. First of all, the literature itself has kind of cherry-picked patients who have the potential for a very good outcome. I mean, the reason that people did ECMO in H1N1 was because the patients were not systemically infected. It was ARDS from a self-terminating viral infection. The patients who were afflicted with it, many of them had an overall excellent prognosis on the other side, whereas, for example, if you take somebody who's got significant underlying comorbidities and ends up with sepsis and ARDS, their chances of benefiting from a run here are much lower.

And, finally, I mean, we saw today images of people getting VV ECMO for COPD exacerbations. And unlike cardiac arrest, which is really not amenable to study, study in populations where there is an accepted alternative therapy like mechanical ventilation are, in fact, doable and should be expected as part of the extension of the respiratory indication. And so for myself, you know, the cardiac indication seems to me to be almost a slam dunk from a classification perspective. The respiratory indication is, in fact, I think where all of the attention to the data needs to be paid. And the data

we have, in fact, is both dirty. So, for example, CESAR has both VV and AV ECMO in it. And it's very selected. I'll stop to give other people a chance.

DR. ZUCKERMAN: Okay. But Dr. Callahan -- I'm sorry -- Dr. O'Connor, you've made some very good points I'd like the Panel to think about. Number one, you've talked about the problems with your interpretation of the respiratory data. Now, certainly, the randomized controlled trial remains the gold standard, but I do want to emphasize to the Panel that data can be acquired in other fashions with well-developed prospective clinical trials.

So the point for the Panel, again, is to respond to where we are, as summarized by your very nice statements, Dr. O'Connor, but not to think that this would necessarily mandate randomized controlled trials for every respiratory indication as opposed to reasonable ways forward for accumulation of real data.

DR. HIRSHFELD: Yeah, Dr. Lange?

DR. LANGE: I'm going to be a dissenting view on this issue of pulmonary. The issue about cardiac, I think is going to be a nonissue. I think all of us would -- I'm going to speak for the group, and people can raise their hands when I say this, but reclassification to Class II is not going to be an issue.

I want to address the two studies. And I've looked at them in detail, so it looks like I'm doing e-mail. I'm not. The CESAR trial was -- we

talked yesterday about how difficult it is to do a randomized controlled trial in the setting of CPR. This is also a setting that's not very easy. And in my opinion, the CESAR trial was probably a terrific trial because it was a real-world experience. In other words, people who were deemed to be suitable for ECMO were referred to a center. And you're right. About 80% received ECMO; 20% didn't. The 20% that didn't had a survival of 82%. The ones that actually got ECMO, their survival was 63% versus 48% of those that did not get ECMO. That was your one hit on that -- or one concern about it.

The second issue was whether they used low-volume ventilation. And as you recall in that study -- you know it better than I do -- is that it was recommended that the centers do that. And 70% of the centers outside in which the patients did not receive ECMO, in fact, did use low ventilation; 90% of the ECMO centers did. It's a real-world trial. I mean, this is exactly what would happen.

So rather than getting a trial where things are perfectly controlled, randomized, non-community based, where we see the very best, and when we translate it into the community, the results aren't so good, I actually think the CESAR trial was very good. And it's limited to people that have ARDS. It's a reversible process. It's not COPD. It's not cystic fibrosis. It's primarily pneumonia. 60% of the patients had pneumonia. So I think it's very good.

With regard to the H1N1 and the Noah trial, they used three

different ways of matching the patients, three different propensity score, and they used a very rigorous sensitivity analysis as well. And I think for the, again, the reasons, the constraints we have with taking someone who has H1N1 and is about to die, you've done everything you can, and your decision is do you continue that process or do you put them on ECMO, I think that it is a very rigorous trial. And by three different matching mechanisms, three different matching scenarios showed the same results, very robust results. So I think in those two patient populations, ARDS and H1N1 resulting in ARDS, I'm convinced the data are very good to reclassify that to Class II. Everything else, I'm not.

DR. HIRSHFELD: Dr. Allen?

DR. ALLEN: So I think that it's interesting to hear the conversation about indications and so forth. And quite honestly, those discussions are in a vacuum of if a device were not already available and out on the market. But, quite honestly, the genie is already out of the bottle. These devices are out. They're being used. And for the most part, they, as Dr. Zuckerman pointed out, they've kind of come in through the back door. And if, for example, you said, no, I don't believe the data, I think that these should all remain Class III devices, quite honestly, nothing would happen because these devices, most of them aren't even approved for this indication anyway. They will stay on the market. They'll continue to be used. The FDA will have no power to try to get their hands on this situation.

Reclassification for both pulmonary and cardiac indications to a Class II will actually encourage companies to come to the FDA to gain marketing advantage by providing the FDA with data. And if they want to get an indication for X process, it doesn't have to be through a randomized trial. The FDA can vet their data, whether it's through ELSO database, whether it's through some other registry, whether it's through investigator run trials. The FDA then can look at that and make good decisions about whether to approve a particular component of an ECMO system for that label.

And that actually, then, helps the clinician because now I can look at data and I can look at the label, and instead of me just kind of picking what I think is the cheapest or the best product, I now have the FDA helping me vet that process with data that then they've reviewed. And I think that's going to be a better system.

DR. HIRSHFELD: Okay. Dr. D'Agostino and then Dr. Cassiere, and then I think we should move to the FDA Questions.

DR. D'AGOSTINO: Just in terms of what I was saying earlier, I think the cardiac is substantial and relatively convincing. None of the trials were beautiful, and so forth, the data and the need and so forth. When you move to the pulmonary, I'm not as convinced as you might be, but I think the pulmonary is showing something. And with this propensity score with replacement and so forth, once you do the "with replacement," you're counting the same person over and over again. If he or she happens to be

healthy, they get -- or survive, they get counted many times. But there's a consistency in the data in terms of what you're seeing. And even if you are willing to say -- or if you're willing to surrender a bit from the statistical significance to are we seeing data that makes sense and going somewhat with the notion of the clinical -- and this is where I have to throw the question out to the rest of the Panel -- the data on the pulmonary I don't believe holds up from a statistics point of view. And I think the FDA reviewers were saying that, or the FDA presenters were saying that also.

But is there enough in that to make us feel comfortable -- and trying to put these studies together is not going to be that easy -- is there enough for us to feel comfortable that there is a sort of signal there? And I would go along with that. And I do a lot of statistics, but I do a lot of making final decision. And I think that this does have a plausibility to it. It's not overwhelming, and we're not going to have one or two studies that we can point to and say, oh, the answer is there.

DR. HIRSHFELD: All right. Dr. Cassiere, and then we're going to move to the Panel Questions.

DR. CASSIERE: I'd just like to respectfully disagree with Dr. Lange. If you take a look at the ARDSNet trial that changed the standard of care for the management of ARDS patients, they were very stringent on their ventilator management. And we all think we do low tidal ventilation, but when you go in and you see what you're really doing, if you don't pay

attention to the numbers, you're really not doing it.

So this trial can be done. And approving a change in the classification from a Class III to a Class II would obviate a PMA that would avoid a trial that actually looks at a standard ventilation profile versus ECMO. ECMO may be better, but the data is not there. You can't say 70% of the centers said they did low tidal ventilation. And everyone around the table who manages critically ill patients, you know, you want to keep their plateau pressures. If you don't follow that like in the ARDSNet trial, you really don't know what tidal volume and what pressures you're generating. So I think you can do a well-designed trial that looks at this particular issue.

DR. HIRSHFELD: Good. Well, this has been a robust discussion, and I think now we're ready -- and this discussion will be further focused by actually going through the well-organized questions that FDA has prepared, because they really are going to lead us right down the path to confronting each of these issues.

Ms. Wentz?

MS. WENTZ: We need to get it up on the screen first. Okay.

Question 1: FDA has identified the following risks to health for extracorporeal circuit and accessories for long-term pulmonary/ cardiopulmonary support, based on the input of the prior classification panels, review of industry responses to the 2009 515(i) order, the Manufacturer and User facility Device Experience, or MAUDE, database,

FDA's literature review, and input from the September 12th, 2013 ECMO panel meeting.

The September 12, 2013 Panel recommended that this is a complete and accurate list of the risks to health for the pediatric populations. Please comment on whether this list remains a complete and accurate list of the risks to health presented by extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support for the adult pulmonary and cardiac populations. Please comment on whether you disagree with inclusion of any of these risks or whether you believe any other risk should be included in the overall risk assessment.

And I'll go back to the other slide so you can see the risks.

DR. HIRSHFELD: Okay. All right. I think I'd like to begin with some of the members of the Panel who have really worked in this area, and I would start with Dr. Zehr. What would your comments be on this?

DR. ZEHR: I think it's a pretty complete list. My question would be should we or should we not add renal failure for the adult population, because I mean, it's a downstream -- it's downstream from hemolysis, but it relates to biocompatibility in the adults.

Go ahead, Keith --

DR. HIRSHFELD: Yes, Dr. Lange?

DR. LANGE: I'm going to comment as a participant on the last meeting. When I look at the voting and what you have up there, there's a

little bit of a disparity, and that is renal dysfunction is listed under hemolysis. That should have been one in September and now. Same thing for DIC. It's listed as a subcomponent of hemorrhage; it should be a separate one.

MS. WENTZ: Correct. Can you tell the rest of the Panel members what page that is in the Executive Summary so they can all turn to it?

DR. LANGE: Well, it's actually on the questions.

MS. WENTZ: Oh, on the questions, okay.

DR. LANGE: Yeah, it's --

DR. HIRSHFELD: There is a questions document, which I think we all have.

DR. LANGE: So just to be more precise, and let me encapsulate what we had talked about in September as well, because we had added renal dysfunction. And it shouldn't be a subpoint. It's its own separate point. Under hemorrhage, it says DIC. That should be a separate subpoint. Under thrombosis/thromboembolism, it says neuro injury. That should be a separate subpoint as well. That's both seen as injury and stroke. And so that would be the clarification.

DR. ZUCKERMAN: Okay. Dr. Allen. Then I'd like to say something.

DR. ALLEN: So I think, though, I have to go back to Catherine's initial definitions of what is a health risk versus what is an adverse event.

And we spent a lot of time in the September panel meeting throwing out things that actually were adverse events, not health risks. And so things like, for example, renal failure, I don't really classify that as a health risk. That's an adverse event related to hemodilution, hemorrhage, mechanical failure, et cetera. So we spent a long time in September vetting these, and I think it is a fairly complete list. And I think what most people are going to come up with are complications, which are adverse events, which don't belong on this list.

DR. HIRSHFELD: Okay. So Dr. Allen, you would include disseminated intravascular coagulation and CNS injury as adverse events?

DR. ALLEN: Those are all adverse events.

DR. HIRSHFELD: Okay.

DR. ALLEN: Somebody has a stroke because of thromboembolism, okay, that's an adverse event, not a health risk. Somebody has leg ischemia because of thromboembolism or thrombosis, that's an adverse event, not a health risk. DIC, et cetera, you can see. So I think we got to go back to what Catherine said at the very beginning.

DR. HIRSHFELD: Okay.

DR. ZUCKERMAN: That's correct, Dr. Allen, or as Dr. Zehr summarized it, when you're talking about downstream effects of what's on that slide, it's an adverse event from the perspective of the regulatory definition. It's not to say that's not important, but we need to separate health risk versus adverse events due to downstream effects.

MS. WENTZ: And if we can address the health risk, then, consequently, we should be able to eliminate those adverse events.

DR. HIRSHFELD: Right.

Yes, Dr. Cigarroa?

DR. CIGARROA: Where would one list metabolic abnormalities?

DR. HIRSHFELD: Any comments?

DR. ALLEN: So metabolic abnormalities, if it were acidosis related to limb ischemia because of thrombosis, it's an adverse event. I think those are adverse events, not health risks.

DR. HIRSHFELD: I think, Dr. Zuckerman, that based on this discussion, the Panel can conclude that the list is comprehensive. There are some adverse events that have been identified that are consequences of these primary risks, so we feel that you do have a comprehensive list.

Is that helpful?

DR. ZUCKERMAN: Yes, it is. Thank you.

DR. HIRSHFELD: All right. Let's move to Question 2.

MS. WENTZ: Question 2: As defined in 21 C.F.R. 860.7(d)(1), there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. As defined in 21 C.F.R. 860.7(e)(1), there is a

reasonable assurance that a device is effective when it can be determined, based on valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

The September 12th, 2013 Panel meeting discussed and agreed that reclassification may be appropriate for ECMO in conditions where imminent death is threatened by respiratory failure in neonates and infants or where cardiopulmonary failure results in the inability to separate from cardiopulmonary bypass following cardiac surgery. Based on our discussions today with respect to the adult population, please comment on whether the available scientific evidence supports an adequate assurance of safety and effectiveness for extracorporeal circuit and accessories for long-term pulmonary and cardiopulmonary support for the adult pulmonary and cardiopulmonary population, as follows:

Question 2a. Do you agree that the available scientific evidence is adequate to support the safety and effectiveness for extracorporeal circuit and accessories for long-term pulmonary support? Remember, this is the adult patient population.

DR. HIRSHFELD: So would you like us to take these step by step, so we'll discuss --

MS. WENTZ: I think so. There are --

DR. HIRSHFELD: We'll discuss 2a first; is that right?

MS. WENTZ: Yes.

DR. HIRSHFELD: So comments on the 2a question?

Yes, Dr. Nathan?

DR. NATHAN: Just to build on the conversation from earlier, pulmonary support is a broad term, and you know, in terms of pulmonary support, I think ECMO has been shown to be a very valuable tool in terms of a bridge to transplant or a bridge to recovery in the case of the flu. It hasn't been studied, I agree, adequately in cystic fibrosis, for example, unless you use it in CF patients as a bridge to transplant. Similarly, for COPD. So when we say pulmonary, it's very broad. I think there are clear indications which are at the discretion of treating physicians, and there are other things that you could put into pulmonary where there isn't any data to support it.

But I guess my question that I pose to the rest of the Panel members is do we take and accept pulmonary, in general, knowing what the indications -- or where the data exists versus these outlying indications where, clearly, there need to be more studies done? And, you know, you can look at many other things that are under Class II devices. I saw one of them being a hemodialysis system, you know, it's used for renal failure, maybe some toxins. But if you use -- and this is obviously an extreme example -- hemodialysis to remove CO_2 for COPD patients, there's no data and it's not an indication.

So when we say pulmonary, I don't know if one can be more specific about this rather than the broad scope of pulmonary.

DR. HIRSHFELD: Other comments? Dr. O'Connor?

DR. O'CONNOR: I agree with what he just said. I think that the use of pulmonary is too vague. I think that the answer to the question globally is no, but I agree with you that, you know, as a bridge to transplant, as a supportive therapy for people with influenza-related respiratory failure, that the evidence is actually fairly convincing.

DR. HIRSHFELD: And, Dr. Cassiere, you've had some comments on this in the past?

DR. KANDZARI: Yeah. I would support that the evidence does endorse the safety and efficacy --

DR. HIRSHFELD: For the record, this is Dr. Kandzari whose name sounds very much like Cassiere.

DR. KANDZARI: Yeah, David. It's interesting to me just in this discussion that the most debate is around the pulmonary indication. There's little question, it seems, so far, at least, with regard to the cardiac issues, and yet so the term "best data," and I use that loosely, is in the pulmonary domain.

I think the challenge for us as a Panel, though, is discerning a regulatory question versus what we would like clinically and what our clinical need is. As Dr. Allen mentioned, these technologies are already available.

They're existent. They will continue to be used. The frequency will likely continue to increase. There are opportunities for us to help shape how that is assessed. But mandating Class II versus Class III is not going to change the quality of evidence or the need for randomized trials, et cetera, that we might want as clinicians. It's not also going to -- it should not discern -- or persuade or dissuade a physician from how he or she wants to care for a particular patient. And that's been well stated. So I would support 2a.

DR. HIRSHFELD: Dr. Cassiere, did you have a comment?

DR. CASSIERE: I was just going to mention I agree with Dr. O'Connor, that for Question a, I don't think I could vote -- I vote no for that.

DR. HIRSHFELD: Okay. So, Dr. Zuckerman, I think I can summarize the comments for Question 2a, that there certainly is feeling among Panel members that the efficacy, the safety and efficacy for long-term pulmonary support is present in certain conditions, and the H1N1 influenza respiratory failure was mentioned as the paradigm of that. But there also is considerable concern that there are a number of other potential respiratory failure indications for which there are lacking data.

Is that helpful?

DR. ZUCKERMAN: That's helpful. But if the pulmonary experts can help us a little bit more. Certainly, you know, I agree with Dr. Nathan that when the FDA gives a label, a general label, it doesn't need to mean that

for every specific possible use, a particular device has been studied, but there needs to be a reasonable basis. And from your perspective, given your knowledge of the literature and actual use of this technology, do you see the word "pulmonary" as being too broad or just right?

DR. NATHAN: I'm trying to think how you can hone that down and make it more specific, you know? It's long-term, you know, for -- it's in the context of respiratory failure when there's another endpoint in sight either as a bridge to something or a bridge to recovery, but I'm not sure how you can encapsulate that in one word.

But I think we have to -- you know, what was said very clearly by the FDA before is, you know, the FDA does the due diligence in terms of approving devices, and then it's up to the clinicians once they're approved how we use it. But I just don't see a situation that if you give -- if you leave it and give that a Class II under the broad scope of pulmonary, that people are going to be rushing out to put a run on ECMO now because it's a Class II indication for pulmonary. I think people -- physicians will still use their discretion and use it appropriately. So I'm actually okay with that unless there's a better way to word it. I think we're leaving a lot to the discretion of treating physicians, which I think is fine.

DR. HIRSHFELD: Dr. Cassiere, were you going to make another comment?

DR. CASSIERE: Yeah. I was just going to make what may sound

like a ludicrous comment, but we could say ECMO is good for cyanide poisoning. They're never going to do a trial to do that. If you want to use ECMO on someone with cyanide poisoning, you can do it. The FDA is not going to stop you. But if the company wants to label an indication for ECMO use for cyanide poisoning, they have to do a study for it. So I think leaving it broad is helpful, and the individual companies that want to market this as a Class III device and have to do a PMA have to pick and choose what indications they want. If it's excellent for cystic fibrosis to bridge them to transplant, you could still that. But if the company wants to label that as such, they should have to do a trial to do that.

DR. HIRSHFELD: Dr. Cigarroa?

DR. CIGARROA: I think as stated, it's too broad for reclassification. Again, this is not dictating how clinicians practice, but with regards to the specific data and the specific use, I think it should be more restricted to the two patient populations in which there is a "reasonable dataset and safety set."

DR. HIRSHFELD: So, Dr. Zuckerman, are we asymptotically getting toward helping you with this?

DR. ZUCKERMAN: Dr. Zehr has his hand up.

DR. ZEHR: What if we just added the word "acute," acute pulmonary failure. I understand that you can lump some other things into acute, but I think the reason I would add that word as a distinction is because

I don't think -- there's very few of us as clinicians that have ever put a -- that have put -- maybe I should say many patients on pulmonary support, ECMO, that were not in imminent danger of dying, you know, within the next 24 hours or so. At least that's, you know, that's been my experience. And I assume it's most people's experience, so --

DR. HIRSHFELD: Dr. Lange?

DR. LANGE: I think it's too broad. I would limit it to ARDS especially with H1N1, and I would say there are other pulmonary conditions that haven't been evaluated that the FDA has highlighted, among them pulmonary emboli, primary pulmonary hypertension, pulmonary parenchymal disease, and even COPD. So if you leave it too broad, all these are included. So I would narrow it to the two studies that show benefit.

DR. HIRSHFELD: Dr. Cigarroa?

DR. CIGARROA: And with regards to data from different registries and single sites, we saw that the uptake in respiratory conditions is a very rapid increase over the last two to three years. We heard from experts who do this, a position of now switching to an ECMO approach at day two or day three when there's not imminent death, but in order to potentially mitigate frailty, the need to paralyze somebody, the need to ventilate somebody. And so I would just push back on that. I think that the desire of certain centers to utilize it earlier is certainly present. We heard that today from the experts. And so I think that we must be more focused and very

specific in this for the reclassification purpose.

DR. NATHAN: I just have to add -- sorry -- Steve Nathan here again -- that, you know, bridge to transplant, it is being used that way. It's gaining a lot of traction. There is good data in the literature. It's not randomized controlled studies, but we don't have those, unfortunately, in the context of lung transplantation. But I think patients can be bridged who have cystic fibrosis, IPF, pulmonary hypertension. So I would just throw that out as well. If we're going to keep it specific, that shouldn't be ignored.

DR. HIRSHFELD: Dr. O'Connor?

DR. O'CONNOR: So I'm wondering if we should just change the wording to a "bridge to transplant" or "for reversible causes of respiratory failure."

DR. ZUCKERMAN: Okay. So let me give a little bit more context because I'd like Panel members also to comment on Dr. O'Connor's suggestion as well as Dr. Zehr's suggestion. Certainly, we don't want to be splitters to the nth degree. And we generally want some reasonable generality to the label, because I would agree with Dr. Cassiere. If a company wanted a specific indication, this could then allow that company to do trials.

So, Dr. Nathan, given what you've heard from Dr. Zehr to perhaps put in acute or from Dr. O'Connor's last comment, is there a bit more specificity that you would suggest without being overly prescriptive?

DR. NATHAN: I think what Dr. O'Connor said kind of

summarizes -- maybe you can repeat -- something in the context of acute reversible respiratory failure or as a bridge to transplant.

DR. O'CONNOR: That's exactly what I said.

DR. NATHAN: Is that good enough?

DR. ZUCKERMAN: Yes. I'd like to hear from other Panel members.

DR. HIRSHFELD: So Dr. Cigarroa?

DR. CIGARROA: So I think moving in that direction is a substantial improvement. My only question to the FDA is with regards to the second aspect, we as a Panel have not seen any data presented with regards to safety or efficacy with regards to the bridge to transplant. And so I don't know how we as a Panel can comment on that other than the individual who has the expertise. So I don't know from a regulatory perspective how we approach that.

DR. HIRSHFELD: Dr. Lange, did you have a comment?

DR. LANGE: Reversible includes COPD. That's my concern, so -- as does CF and a number of others which haven't been studied.

DR. O'CONNOR: This is Michael O'Connor. I mean, so for myself, I share your quandary about COPD. Somebody who has a COPD exacerbation may be reversible or they may be hospitalized for the irreversible progression of their disease. And the decision as to which of those is, in fact, present I think is ultimately up to their bedside caregivers.

But, you know, like I said, I mean if somebody is discharged from the hospital after a three-day admission for COPD that included veno-venous ECMO, you got to ask yourself, is that something we should ask them to study before we agree to let people do it on a widespread basis.

DR. NATHAN: Steve Nathan again. Maybe another way to get around that, to avoid those folks is throw in the word "hypoxic," acute hypoxic respiratory failure, which would be unusual for COPD patients and would be more specific for ARDS type patients.

DR. HIRSHFELD: Dr. Allen?

DR. ALLEN: So I think Dr. Zuckerman actually summarized it very well. I think micromanaging disease states during this reclassification problem -- process is a mistake. I think you -- it's like porridge. I think the word "pulmonary" is probably just right. I think if you begin to parse out specific disease states, I don't think there's -- the totality of the evidence doesn't necessarily allow you to do that. And I think this, by keeping it broader and not micromanaging, not naming specific disease states, you allow the FDA through special controls to label devices that companies bring to them for, then, specific indications. You don't handcuff the FDA, and you also don't handcuff companies and allow them to do their job. And I think that's a better way.

DR. HIRSHFELD: Yes, Dr. Good?

DR. GOOD: Well, this is Dr. Good. I'm going to jump here in an

area that I don't really deal with much, but what about some sort of a qualifier here saying that this is appropriate where other standard therapies have failed or are not applicable; something like that that would be a little bit broad that would cover some of these other areas and still not handcuff the individual clinician. Just a thought.

DR. HIRSHFELD: Dr. Cigarroa?

DR. CIGARROA: The issue is that this is standard therapy under certain scenarios in clinical practice in certain centers. And I think that's where, I think, Dr. Zuckerman mentioned data and then experience within the clinical practice. And so I think that's the challenge with trying to word it in such a way.

DR. ZUCKERMAN: Okay. So this is a very difficult process, and we don't want you to spend excessive time trying to wordsmith something. I think we got the point. But as a final summary, Dr. O'Connor, you appreciated the tension here between being too specific and too broad. And can you just repeat your suggestion and see how people respond to it?

DR. O'CONNOR: Well, my original suggestion was bridge to transplant or reversible causes of respiratory failure. I liked Dr. Nathan's suggestion that we could perhaps include acute hypoxic, but I don't feel strongly one way or the other. I'd defer to the expertise of everyone else in the room as to which of those people thought was appropriate.

DR. HIRSHFELD: Dr. Cassiere?

DR. CASSIERE: I'm going to agree with Dr. Allen. We should not parse out what disease states. I think we should be broad and let the FDA and companies figure out what indications that they want to have the devices for.

DR. HIRSHFELD: I think, as I've been listening to this -- this is Dr. Hirshfeld -- what I've been hearing is that we all agree that it works that if someone has acute respiratory failure and you basically do pulmonary replacement with veno-venous ECMO, that you normalize oxygenation and CO_2 parameters, and so you at least buff the patient up. What's a lot less certain is when does it make a long-term difference in long-term outcomes. And so I think what -- and this is really the crux of the problem, that there are some patients in whom it may really enhance survival with good functionality. There are other patients in whom it -- who would have survived without it. And there is a third group or patients who won't survive with it or without it. And that's really the crux of the issue as far as the indication. And, really, the second part of the -- the next part of the question as well. But I think that's -- I'd like to suggest that as an encapsulation of the basis of the conundrum that we've been wrestling with.

Does that make sense to the rest of the group?

(No response.)

DR. HIRSHFELD: So, Dr. Zuckerman, have we helped you with Question 2a?

DR. ZUCKERMAN: Yes.

DR. HIRSHFELD: Sort of.

DR. ZUCKERMAN: Dr. Allen, did you have any final comments? You had your light.

DR. ALLEN: I actually like "acute respiratory failure." I think that is broad but also takes into account -- maybe is a tad bit more specific. I would take out "bridge to transplant," though. I don't know if -- you know, I think that seems not unreasonable if you want to be -- so I don't mind that language.

DR. NATHAN: If you just keep it "acute respiratory" or "acute hypoxic respiratory failure," I mean, that encapsulates bridge to transplant in actual fact.

DR. HIRSHFELD: Dr. Cigarroa?

DR. CIGARROA: Just a question to the pulmonary experts on the Panel. The distinction -- I understand the hypoxic, but the acute hypoxic respiratory failure, the distinction between including hypoxic versus not in terms of handcuffs, et cetera?

DR. NATHAN: Well, if you say acute respiratory failure, it can be hypoxic or hypercapnic, like COPD exacerbation.

DR. CIGARROA: That's my point, so I think if we go that direction, including the word "hypoxic" would be important.

DR. ZUCKERMAN: Okay. I think we've got in a lot of good

comments in here, Dr. Hirshfeld. Thank you.

DR. HIRSHFELD: Okay. I'd like to provide you better clarity if we could.

Okay. So let's go to Question 2b.

MS. WENTZ: Question 2b: Do the probable benefits to health from use of the extracorporeal circuit and accessories for long-term pulmonary support outweigh the probable risks to health?

DR. HIRSHFELD: Comments from the Panel on this?

Yes, Dr. O'Connor?

DR. O'CONNOR: Based on how we've answered Question 2a, I think the answer is yes.

DR. HIRSHFELD: That was quicker than Question 2a, so I think the Panel generally believes the answer is yes.

DR. ZUCKERMAN: Thank you.

DR. HIRSHFELD: Okay. Question 2c?

MS. WENTZ: Question 2c --

DR. LASCHINGER: Can I ask a question about 2b first? Should we change the terminology to the same terminology we're going to use for 2a?

DR. ALLEN: Yes.

DR. HIRSHFELD: Yes, I see the Panel members nodding.

MS. WENTZ: Thank you. Okay. Question 2c --

DR. NATHAN: Sorry. Just coming back to that. Just when you say long-term acute hypoxic respiratory failure, it just -- it's like oil and water, I think.

DR. LASCHINGER: I would say "long-term support of acute hypoxic pulmonary failure" as the phrase, not just add the word "acute." I would change the order of the words also.

MS. WENTZ: Okay. Question 2c: Do you agree that the available scientific evidence is adequate to support the safety and effectiveness for extracorporeal circuit and accessories for long-term cardiopulmonary support?

DR. HIRSHFELD: Okay. Are there comments on this one? We're now going to the heart?

Dr. Cigarroa?

DR. CIGARROA: So, one, I would change the term cardiopulmonary to cardiac, and two, I think the answer is yes for the majority of acute cardiac decompensation. I am certainly uncertain and unimpressed by the data in the emergent CPR group, and that would be my only asterisk.

DR. HIRSHFELD: Dr. Allen?

DR. ALLEN: I don't think you can take out pulmonary because you have to cut -- it's very rare that you put somebody on pure cardiac support. You have to cut in an oxygenator. So it's just not possible.

DR. HIRSHFELD: Dr. Zehr?

DR. ZEHR: Yes, Kenton Zehr. I agree 100%. I mean, just by virtue of where your cannulas are, you know, you're bypassing both the heart and the lungs, and so -- and the definition of ECMO has become cutting an oxygenator into the system. Otherwise, we're a VAD.

DR. HIRSHFELD: Yeah, Dr. Cigarroa?

DR. CIGARROA: I think I confused the situation a bit in that I meant that the use of long-term cardiopulmonary support by an ECMO circuit is effective in patients who have a primary acute cardiac decompensation is what I meant.

DR. HIRSHFELD: I think we all understand that.

Yeah, Dr. Cassiere?

DR. CASSIERE: Yeah, I just want to echo that, that it's cardiac failure that's prompting the cardiopulmonary support. Keeping the cardiopulmonary support in there leaves wiggle room that you could use it for pulmonary support. That's my only concern. I agree with Dr. Lange with that.

DR. HIRSHFELD: Okay. Could we perhaps suggest that it would say "long-term cardiopulmonary support for intractable cardiac failure"?

DR. ZUCKERMAN: Catherine, do you want to comment on that?

DR. HIRSHFELD: Yeah, Catherine, would that be constructive or

not constructive to reword that --

MS. WENTZ: No, I think that would be constructive. We need to stay away from the VAD category, which is pure cardiac failure.

DR. HIRSHFELD: Okay. All right.

Dr. Good?

DR. GOOD: The term "long-term," is that the correct term here? It's a little bit different than pulmonary. Most of the cardiac situations are much shorter than -- like 24 hours, something like that. So is that term appropriate?

DR. HIRSHFELD: Dr. Lange?

DR. LANGE: So let me -- for long-term support for acute, long-term support, meaning more than 24 hours, for an acute catastrophic primary cardiac event, referring to your slide on 47 for the FDA.

DR. HIRSHFELD: Um-hum.

MS. WENTZ: And I would also like to clarify that we are proposing to redefine long-term --

DR. LANGE: Six hours?

MS. WENTZ: -- as anything over six hours.

DR. LANGE: Yeah.

DR. HIRSHFELD: Yeah.

Dr. O'Connor?

DR. O'CONNOR: So my direct experience is that patients who

fail to separate from bypass often require two weeks of support. And Dr. Zehr, you stated earlier today that your median duration is 16 days. So I would actually argue in favor of long-term, and I liked, as I mentioned previously, the 16-day or 32-day duration.

DR. HIRSHFELD: Yes, Dr. Zehr?

DR. ZEHR: I would like to clarify that that included VV as well as VA. The shorter runs are VA. I want to make one point regarding cardiopulmonary failure. Frequently, the two go -- cardiac and pulmonary -- frequently, the two go hand in hand. You have primary cardiac failure. You have low flow. You have hypoxic decompensation. So the two indications are frequently hand in hand. And then the other issue comes up where the indication for ECMO being major trauma, which is combined cardiac and pulmonary failure. And most ECMO series have a fair number of those patients in their series. So, you know, once again, I hate to parse out various diseases here, and I think we should keep it broad. And I think we need to make a strong distinction between VAD therapy and ECMO therapy.

DR. HIRSHFELD: Okay.

Dr. Allen?

DR. ALLEN: Yeah. I think if you separate cardiopulmonary, you walk a dangerous course of moving to a VAD. You really do. I mean, a VAD does not take into account pulmonary. ECMO does. So what Ken is saying is completely correct in the VAD world and ECMO world. Really, they go hand

in hand. I don't think you can separate them.

DR. HIRSHFELD: Although I think that we are frequently, in this application, we're frequently considering it a bridge to something else, one of which would be a VAD?

DR. ALLEN: No, a bridge to something else is a -- if you bridge somebody, I put a PVAD in. If I need right ventricular support, I put a VAD in. I don't -- or I have an LV support, I put a VAD in, and there are VADs that I can use, and I can bridge people with a VAD. But that's not what we're talking about with ECMO. ECMO is cardiopulmonary support with an oxygenator and a pump, and that is not a VAD. Very different.

DR. HIRSHFELD: Dr. Lange, did you have a comment?

DR. LANGE: No --

DR. HIRSHFELD: Oh --

DR. LANGE: So there are two independent things. One is the term "long-term cardiopulmonary support." That indicates the device system for more than six hours. And the indication is for an acute cardiac event. And that cardiac event has many manifestations. Could be a low output, could be hypoxia, could be for whatever, but that's the -- as opposed to -- that distinguishes from a VAD.

DR. ALLEN: No. A long-term use of a device for an acute cardiac event is a VAD. A VAD does not include an oxygenator. So an acute long-term -- if you put a patient in and bridge them for an acute cardiac

event, you put a VAD in that patient, but cardiopulmonary support with an ECMO device takes just what Dr. Zehr said into account, that it often goes hand in hand. They're very different.

DR. HIRSHFELD: Okay.

Dr. Cigarroa?

DR. CIGARROA: I think the discussion comes back to FDA slide 47 entitled "Cardiogenic Shock and Heart Failure" in which the super category is cardiogenic shock and heart failure, and then there is a acute catastrophic cardiogenic shock, which is what I think we're focused on right now in terms of the cardiopulmonary. Then there's subacute. And then there's chronic. My only point is that this should focus on acute catastrophic cardiogenic shock of which there are several different etiologies. And so if it's phrased accordingly, then I think that we're all fine.

DR. ZEHR: Kenton Zehr. Can we do that by saying "cardiopulmonary support for acute catastrophic cardiogenic shock"?

DR. CIGARROA: I would think so.

DR. HIRSHFELD: Any other comments on that? Yeah, Dr. Nathan?

DR. NATHAN: I'm just not sure, you know, trying to keep it simple, I'm not sure you need to have catastrophic in there. I mean --

DR. HIRSHFELD: Yeah.

DR. ZEHR: Well, it's catastrophic in the sense that if you don't

put the -- if you don't them on ECMO, they don't survive.

DR. NATHAN: I guess it's that balance between being too prescriptive, and you don't want people standing around saying, well, is this catastrophic or not. You know, people know when to put it in.

DR. ZEHR: I think we know when it's catastrophic.

DR. HIRSHFELD: So I think that although we've had some fine tuning, I think, Dr. Zuckerman, I think I can summarize the opinion of the Panel that they agree that ECMO is safe and effective for the -- for long-term cardiopulmonary support.

DR. ZUCKERMAN: Thank you, Dr. Hirshfeld. This has been a very good discussion here.

DR. HIRSHFELD: Okay. And, finally, Question 2d?

MS. WENTZ: Okay. Question 2d: Do the probable benefits to health from use of the extracorporeal circuit and accessories for long-term cardiopulmonary support outweigh the probably risks to health?

DR. HIRSHFELD: Comments? I think we actually answered this question at the same time we answered Question 2c, so the answer is yes.

DR. ZUCKERMAN: Thank you.

DR. HIRSHFELD: All right. We will move on to Question 3.

MS. WENTZ: Question 3: For those populations where the available scientific evidence supports an adequate assurance of safety and effectiveness and the probable benefits to health outweigh the probable

risks, it may be feasible to establish special controls to mitigate the identified risks to health (outlined in Panel Question 1). Following are potential special controls FDA could establish to mitigate the risks to health presented by ECMO for the adult pulmonary and/or cardiopulmonary populations (this list is the same as for the pediatric special controls
discussed during the September 12th, 2013 Panel meeting, and presented on pages 14-15 of the Executive Summary). They are as follows:

- The design characteristics of the device must ensure that the geometry and design parameters are consistent with the intended use.

- The devices must be demonstrated to be biocompatible.

- Sterility and shelf-life testing must demonstrate the sterility of patient contact and components and the shelf-life of these components.

- Nonclinical performance evaluation of the device must demonstrate substantial equivalence in terms of safety and effectiveness for performance characteristics on the bench, mechanical integrity, EMC (where applicable), software, durability, reliability, et cetera.

- In vivo evaluation of the device must demonstrate device performance over the intended duration of use and for the specific indication.

- And, finally, labeling must include a detailed summary of the nonclinical and clinical evaluations pertinent to use of the device and adequate instructions with respect to anticoagulation, circuit setup,

performance characteristics with respect to compatibility with other circuit components, and maintenance during the procedure.

Please comment on whether these special controls are adequate to mitigate the risks to health for extracorporeal circuit and accessories when used as intended, and provide sufficient evidence of safety and effectiveness for:

a. Long-term pulmonary support in the adult patient population; and/or

b. Long-term cardiopulmonary support in the adult patient population.

Please comment on whether you disagree with inclusion of any of these special controls, or whether you believe any other special controls are necessary.

DR. HIRSHFELD: Okay. Dr. Kandzari?

DR. KANDZARI: Okay. David Kandzari. I think the special controls are adequate with one exception. This really represents a large opportunity for surveillance, clinical surveillance, and whether it's through ELSO, ACC, NCDR, or some other -- or just separate independent sponsored registry to help satisfy many of the outstanding concerns of the Panel, and recognizing the limitations that we've already heard of a modest, probably a modest number of contributors to registries like ELSO, and not having the incentives to do that necessarily, or perhaps being challenged by the finances

of doing it, I think here is the opportunity for surveillance.

And this is especially relevant because for all of the -- and in parallel, the clinical community will foster its own generation of evidence in the specific niche indications that have been discussed particularly in the pulmonary realm. But when we talk about these technologies, ECMO, being represented probably by many separate companies as sponsors of devices, it makes it very challenging, sometimes impractical to do a trial if you make the cannula but you're dependent on somebody for the oxygenator or the pump. Here, I think everyone can contribute to sponsoring better evidence through a registry.

DR. HIRSHFELD: Okay.

Yes, Dr. Brindis?

DR. BRINDIS: So this is why I asked FDA earlier what we had put in place from the previous panel for pediatric group, because just like David had mentioned, what is listed here does not talk about surveillance mechanisms within a registry in the pediatric group, which I had asked specifically.

And I want to echo David's comments. This is an incredible opportunity here not only for postmarket surveillance in terms of device failure, but also in terms of understanding best practices. When you think about the orthopedic world with hip devices, there are many different components related to that, and the only way one can actually assess -- and

clinicians use different components interchangeably. So to be able to have a way of following in a registry format all the different components, for example, in an ECMO environment, may give us substantial understanding. The opportunity to do observational work, even nested studies in terms of the subgroup of concern that we have in the pulmonary space is also a great opportunity.

Challenges that we've already identified on the Panel include the carrots and sticks in participation and also the issues related to the quality of the data. And then the next question is what oversight does the FDA have even to be able to mandate such a participation if a registry format comes into play?

You know, there are a lot of stakeholders, not just companies, that would be very interested in this data, particularly as we were just learning, about the marked expansion, for example, in the pulmonary space. So needless to say, that comes to mind the payers and the purchasers, whether it be CMS or private payers. And you would think trying to get them sitting at the table and appreciating the value to the data for them in terms of understanding where we need to be going and not taking our technology in places that have no efficacy is an opportunity.

So I strongly endorse, in other words, the concept of using registries. I was very impressed with the presentation of ELSO with the appreciation that it's voluntary, we don't have a broad representation of all

the players, we need to increase its quality, and we need to work on the carrots and sticks for participation.

DR. HIRSHFELD: Okay.

Dr. Allen?

DR. ALLEN: I'm going to take the contrary in that I think registries give us a false sense of security. Registries, by nature, are voluntary. They're usually unaudited. There's little to no enforcement that goes into what goes into the registry. And while they make us feel good, we then oftentimes act on registry data. I hearken back to the HeartWare trial with the use of INTERMACS and the issues that were discussed at that panel in using INTERMACS data for that trial. We think it's good data, but because it's voluntary and unaudited, I'm very much underwhelmed by it. And I'm not sure how you can enforce or pay or do that. And so I would not be inclined to put that in as a special control.

DR. HIRSHFELD: Okay.

Dr. Cigarroa?

DR. CIGARROA: So I think that, you know, registries have inherent limitations. That said, if one establishes a series of best practices to mitigate, then I think they can be exceedingly useful. Secondarily, where the data that is compelling us to reclassify, which I think that there is data that would support that, that data is not the most robust. The fact that we are making that data with approximately 50% of patients receiving these

therapies not being included behooves us to, A, ask the FDA to see whether or not registry -- whether participation in a registry can be done, and if so, how should it be done from a best practice.

I think I take a look at the HeartWare panel that several of us sat on as an opportunity of lessons learned on how registries can be utilized for patients who have exceedingly high probabilities of mortality if you don't have another therapy. But, two, the panel discussion I think elucidated several best practices that could be put in place so that the FDA and we as clinicians can have a better reliance on the data and the analysis that the registries are then able to have as an output.

DR. HIRSHFELD: Dr. O'Connor?

DR. O'CONNOR: So my answer to the questions is with respect to (a), I don't know. And with respect to (b), I think the special considerations that the FDA has outlined here is, in fact, more than sufficient for the cardiopulmonary support device.

DR. HIRSHFELD: Okay. Can you clarify what you mean by you don't know for (a)?

DR. O'CONNOR: So it sounds really silly, but I don't think we have enough data about the respiratory indication, the pulmonary indication, for us to even have a sense whether these and a registry would suffice. I think we need more data before we could even answer that question.

DR. HIRSHFELD: So, Ralph, you had a comment?

DR. BRINDIS: I feel obligated to respond to Dr. Allen, and I admit my conflict of interest in being the Senior Medical Officer for the National Cardiovascular Data Registry. And I acknowledge the challenge with voluntary registries that are unaudited and the quality of the data.

But we as a nation have become increasingly comfortable both on a regulatory basis, at CMS and particularly in the FDA, related to the quality of the data in the National Cardiovascular Data Registry and other registries to the point that we've had numerous publications related to the quality of the data. We have a robust auditing function, a robust adjudicating function, to the point that in partnership with the FDA, we're taking on in our registry both PMS studies and also IDE studies. And I don't think the FDA would utilize the NCDR if they thought the quality of the data was poor.

DR. HIRSHFELD: Okay.

Yes, Dr. Nathan?

DR. NATHAN: I'm a fan of registries, and I think there's a lot of information that can come out of them. But if you read very carefully what the FDA is looking for with their question, whether the controls are adequate to mitigate the risk to health for extracorporeal circuit, and it says here, when used as intended, I don't think a registry is necessary for that, because I think what we're all after with the registry is to make sure it's used appropriately, what the indications are, et cetera, et cetera. So I think what's in place is adequate independent of a registry. Do I think a registry should happen in

any event? Yes, I do. I think it can provide valuable information, but not as pertains to what the FDA is after under Question 3.

DR. HIRSHFELD: So, Dr. Zuckerman, I think Dr. Nathan just summarized what I was going to say in summary of our discussion, which is namely that I think the Panel believes that the listed special controls are sufficient. The Panel has also expressed a strong desire that there be a forward-looking data gathering of real-world experience as part of this undertaking.

DR. ZUCKERMAN: Okay. Dr. Nathan read the question very well, and his response was excellent. But let me ask you this. I mean, you're right. It really depends on what questions we want answered. And, initially, there was some discussion about what did we make out of the recall and MDR data. And because we don't have a denominator and there's underreporting, that phase of potential postmarket surveillance is often problematic. Given that a special control such as a postmarket surveillance might be able to help better answer that sort of question, are you still confident that consideration of postmarket surveillance special control might not be necessary?

DR. HIRSHFELD: My impression was that the Panel felt that postmarket surveillance was very important, and whether that would be lumped under the rubric of a special control would be a regulatory decision.

Is that stating what the Panel feels? Got a few hands.

Dr. Cigarroa?

DR. CIGARROA: So I have two comments. One is yes. Two, as you read the question very carefully, as intended, there is a heterogeneity, I think, in the Panel's sense of belief with regards to the data in pulmonary. I think that various individuals have expressed specific disease states and whether that dataset even in those disease states is sufficient enough. And so although I recognize the importance of the term "as intended," my belief for participation in a state-of-the-art registry is, in part, to provide further insights into these particular patient subgroups. So there is the issue of safety, et cetera, from device manufacturers and recalls, and then there is the issue of how is the device being -- how is the circuit being employed and what insights are we able to obtain from a registry regarding outcomes and variation of outcomes.

DR. HIRSHFELD: Yes, Dr. Allen?

DR. ALLEN: So I hearken back to the fact that we're not talking about a single system. This is a -- these circuits have 10 or 12 or 15 different components. How does a registry that tracks -- it's like MDRs. You have no clue -- you get an MDR, and we don't know that the pump failed or the oxygenator failed or a cannula failed. How are you going to track this in an accurate fashion? It's one thing if it's one product, but this isn't one product we're talking about. It's 10 different products. It makes us feel good to talk about it, but the practicality and the useful information that we're going to

get from it, I think, is going to be very limited.

DR. HIRSHFELD: Yes, Dr. Good?

DR. GOOD: So you still have the MDR reports to deal with some of the product failures. But I think it would be a mistake to lose the opportunity to make sure that we don't endorse a well-designed registry. We already have the ELSO registry. I'm a little concerned how that's going to work. It's a not-for-profit organization, it's voluntary, but at least it's something possibly to build on.

DR. HIRSHFELD: Okay. So, Dr. Zuckerman, have we helped you some with this?

DR. ZUCKERMAN: Yes. I think Dr. Nathan may have wanted to make a closing comment.

DR. HIRSHFELD: Okay.

DR. NATHAN: Well, the one thing I was thinking was if, you know, you can't impose a registry, I guess, it would be volitional. But on the other hand, I'm hearing that there might be 16 parts to an individual setup. Does it become, actually, an impediment to implementing ECMO that, you know, the thought goes through the back of people's head, oh, my gosh, I've got to -- you know, I don't have a nurse coordinator to help me; who's going to fill out the registry data; you know, we're going to get by without this. So it shouldn't be a thing that drives the use, but I do wonder about the integrity of the data if it's going to be that complex. But, once again, I think as an

aside, you know, maybe the existing registry will give us more of the information that we want with the inherent biases that, you know, who's contributing to that registry. But, you know, I think you can certainly argue it both ways.

But when we look at this, and you know, with the intended use, I think there's got to be other ways of getting at that intended use, because if a registry is volitional and people don't contribute all the data, then invariably what's going to happen is that those patients who are marginal candidates and wouldn't fall under what we regard as intended use wouldn't make their way into the registry.

DR. HIRSHFELD: So, Dr. Zuckerman, is this sufficient for FDA's needs?

DR. ZUCKERMAN: This has been a good discussion, but how would you summarize what you've heard?

DR. HIRSHFELD: I think I would summarize that the Panel is comfortable with the listed special controls that have been listed in the question, that they feel that they're appropriate, necessary, and reasonably comprehensive in terms of the operational aspect of this system. The Panel has expressed considerable concern that, at multiple levels, it's important for the medical community to understand exactly what's being achieved with these endeavors, and that that -- not only from the standpoint of whether or not there are potential future device-related problems, and also whether the

entire -- the appropriateness of the entire enterprise. And for that regard, we've heard a number of different calls for various types of systematic collection of outcome data from patients who undergo these procedures.

DR. ZUCKERMAN: Okay. Thank you.

DR. HIRSHFELD: Okay. All right.

Catherine?

MS. WENTZ: I think I read (b), but I'll read it again. I'll read the beginning and then (b).

Please comment on whether these special controls are adequate to mitigate the risks to health for extracorporeal circuit and accessories when used as intended, and provide sufficient evidence of safety and effectiveness for long-term cardiopulmonary support in the adult patient population.

Please comment on whether you disagree with inclusion of any of these special controls, or whether you believe any other special controls are necessary.

DR. HIRSHFELD: Okay. So this is similar to (a) except applied to the cardiopulmonary dimension. Does any Panel members have any comments about this applied to cardiopulmonary, or can we cut and paste from what we've done already? I see several heads nodding that cutting and pasting will work for this.

Is that satisfactory for the FDA, Dr. Zuckerman?

DR. ZUCKERMAN: Yes.

DR. HIRSHFELD: Okay. All right. Now Question 4.

MS. WENTZ: Question 4: 21 C.F.R. 860.93 describes the classification of implants, life-supporting or life-sustaining devices and states that "the classification panel will recommend classification into class III of any implant or life-supporting or life-sustaining device unless the panel determines that such classification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. If the panel recommends classification or reclassification of such a device into a class other than class III, it shall set forth in its recommendation the reasons for so doing. . ." FDA believes that extracorporeal circuit and accessories for long-term pulmonary/cardiopulmonary support are life-supporting, which was supported by previous classification panel recommendations for membrane lung for long-term pulmonary support.

Question 4a: Do you agree that extracorporeal circuit and accessories for long-term pulmonary support are life-supporting?

And b: Do you agree that extracorporeal circuit and accessories for long-term cardiopulmonary support are life-supporting?

DR. HIRSHFELD: Panel comments?

DR. ALLEN: Yes --

DR. HIRSHFELD: I see heads nodding. Are there any heads shaking? I see no heads shaking. So, Dr. Zuckerman, we can say confidently

that the Panel feels that the answers to Question 4a and 4b are both yes.

DR. ZUCKERMAN: Thank you.

MS. WENTZ: Question 4 continued: If there is sufficient information to establish special controls to provide reasonable assurance of the safety and effectiveness of the device, in conjunction with general controls, the device would be appropriately classified into class II. If insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness, the device would be appropriately classified into class III.

Based on the available scientific evidence and proposed special controls, what classification would you recommend for extracorporeal circuit and accessories for long-term pulmonary support for the adult patient population?

DR. HIRSHFELD: Okay. So this is getting down to the real final part of this process. And I think it would be constructive for us to hear from each of the voting members of the Panel to hear their thoughts about this particular issue. This is not really, I guess, an official Panel vote, but I think each member of the Panel should have an opportunity to express their opinion about this.

So I will start with Dr. O'Connor.

DR. O'CONNOR: I'm just going to point out that I'm listed as a non-voting member.

DR. HIRSHFELD: I think that's not correct.

DR. ZUCKERMAN: That isn't -- Dr. Hirshfeld is correct. We just need your opinion here. It's an important one.

DR. HIRSHFELD: Yes.

DR. O'CONNOR: Got it. So for myself, with respect to 4c, I think that the evidence is not sufficient for a reclassification. With respect to 4d, I think the evidence is, in fact, sufficient for reclassification. I think that you can go to Class II with special controls. And I have nothing to say about 4e.

DR. HIRSHFELD: Yes, Mr. Branson?

MR. BRANSON: So this is my second panel, so I'm sorry I'm not that experienced. I'm having a issue of what's going to be the long-term outcome. I've heard one Panel member say if we go to Class II, FDA is going to have more control. And then we have another Panel member who's concerned if we go to Class II, it's going to open the doors even wider. And we saw from our experts who are very passionate about how important ECMO is and how much they use it, but they're out here, and there's a continued use.

Can somebody from FDA answer that question for me? Would there be greater control or greater oversight if it were Class II than Class III? Again, I apologize if I don't understand.

MS. WENTZ: No, this is very confusing. Good question. Again,

it goes back to having enough valid scientific evidence to determine that there's enough safety and effectiveness data out there to reclassify the device to Class II. If we're already assured that the device for that intended use is safe and effective, then it can go into the 510(k) category, where there is less oversight than the PMA category as far as the requirements, manufacturing, things like that.

If we decide that there isn't enough safety and effectiveness data, then it would remain in Class III. It would require a PMA, which is generally clinical studies and more oversight than a 510(k).

MR. BRANSON: So it makes sense to me that if it's safe for cardiopulmonary support, then it has to also be safe for pulmonary support. I think our issue is effectiveness.

DR. HIRSHFELD: That's correct.

MR. BRANSON: It's probably -- it's safe and effective in cardiopulmonary. It's safe in pulmonary, but we don't know if it's effective or not. And, again, then I guess I'd listen to other Panel members about -- because I can tell you, there is a lot of push in every hospital to do ECMO. Everybody wants to do ECMO. Everybody wants to be seen as being on cutting edge. And I wonder if they're Class II, if the companies will push it further, and is that really our concern? I don't know.

DR. HIRSHFELD: So are you saying no for (c) and yes for (d)? Is that --

MR. BRANSON: Yes, sir.

DR. HIRSHFELD: Okay. All right.

DR. ZUCKERMAN: Okay. But let's clarify again what Catherine is asking in this question. And I fully understand everyone's concern about Pandora being out of the box. But we need to take this in steps. And the first step is just to look at the safety and effectiveness data and make that determination whether you think it's Class III or Class II. Then there's a different component, which is what happens if a firm then inappropriately advertises or sells the system. And as Catherine explained previously, that's a issue that's taken seriously by the FDA. And there is a specific Office of Compliance that polices the many circumstances that occur in that category. But let's first just focus on the data in the safety and effectiveness issue.

DR. HIRSHFELD: Yes, I understand. Ralph, I'd like you to speak next, please.

DR. BRINDIS: Yeah, thanks, John. Ralph Brindis. My votes would be that from the cardiopulmonary support mechanism indication for cardiac indications, that it could be moved successfully into a Class II, and that for a pulmonary indication, if you had appropriate oversight related to registry evaluations that the FDA was comfortable with to be able to assess different indications, you could move it into a Class II. But if you do not, then I would suggest keeping it as a Class III.

DR. HIRSHFELD: Okay. Thank you.

I will go back to Dr. Good.

DR. GOOD: Thanks very much. I've been listening to this all morning. And it's been interesting conversation. I would say that for (d), I agree, that it could be reclassified into a Class II. For (c), as everybody has pointed out, it's more difficult. There are so many different conditions here. I think the evidence of effectiveness is probably different for these different conditions, as many of the people around this table have said. I think, also, it could be a Class II, though, again, if there are effective controls from the FDA. I'm concerned that if it's Class III, from a regulatory point of view, and I realize that's not our role, I don't know how the FDA would even do this because there's so many different companies and so many different components, it would just seem that it's unreasonable to get your arms around it. But that's not our decision.

So I would say that as long as -- that it could be a Class II. I agree completely with Dr. Brindis that there should be some way to collect information on this, preferably through a registry.

DR. HIRSHFELD: Dr. D'Agostino?

DR. D'AGOSTINO: Ralph D'Agostino. I believe that II is appropriate for both the (c) and (d). I'm very impressed by the cardiopulmonary, and clearly, it's a II, but -- for me. As far as the pulmonary, there are issues. The data is not substantial. The signal that is there is in the right direction. But I do think the controls that we're talking about in terms

of registries and what have you would be a way of dealing with that. And my II classification -- and I think I'm saying what other people have just said -- the II classification carries with it that there are going to be these type of controls.

DR. HIRSHFELD: Okay.

Dr. Zehr?

DR. ZEHR: I think that in some ways, the national exuberance speaks for itself, and we now have therapies in both pulmonary and cardiopulmonary support, which is an alternative to death. It's very interesting about the paradox of all this is because our best results are with the pulmonary side, and any ECMO program, I think, will say that. And our highest complication profiles and our worst results are the cardiopulmonary support. Certainly, the complication profiles are worse. And I strongly support moving this to Class II for both arenas. I think, to coin Dr. Allen's phrase, the cat is out of the bag. I think this will allow more -- excuse me -- I think this will allow more regulatory control, as companies will have to prove their components for longer term use. And, in fact, maybe we'll finally be able to use ECMO therapy without -- within an appropriate regulatory pathway. Thank you.

DR. HIRSHFELD: Okay.

Dr. Allen?

DR. ALLEN: Yeah. I think probably everybody knows how I feel.

Pandora's box is already open. In fact, the box had disintegrated. And so I would agree that these could be reclassified both for cardiopulmonary as well as pulmonary to a level II. I think special controls that the FDA can institute will allow appropriate regulation and oversight, and in fact, I think we will have better regulation to prevent backdoor use of devices than if you don't down-classify it.

DR. HIRSHFELD: Dr. Lange?

DR. LANGE: I'd say II for both, and specifically for pulmonary with regard to the specific indications in which we have studies. And, again, I want to echo what my colleagues said. Studies are best. The only one randomized controlled trial was the pulmonary. And I came here not expecting to be very convinced by the data, but I've looked at the studies in detail, and I think the studies are actually pretty good. They're not perfect, but we haven't yet seen a perfect study. So I vote II for both with specific limitations for the acute hypoxic respiratory indication.

DR. HIRSHFELD: Dr. Cigarroa?

DR. CIGARROA: Agree with the comments that Dr. Lange stated, yes and yes, reclassification with special controls.

DR. HIRSHFELD: Okay. And Dr. Cassiere?

DR. CASSIERE: Dr. Cassiere here. I agree with (d), to reclassify as a Class II, but I disagree with (c). I don't believe the data in the pulmonary realm has really shown that it should be classified as II, and companies should

come and present data if they want their product approved for a specific indication. And I agree that there was a good randomized trial, but it takes more data to change -- try to change the standard of care.

DR. HIRSHFELD: Okay.

Dr. Yuh?

DR. YUH: Yes. I would be in favor of moving for both indications to Class II. I'm actually surprised that I've actually changed my stance on pulmonary, but like Dr. Lange, I was impressed with the quality of the data and the superiority of general outcomes in its pulmonary application. So it moved me to not split the classification and to go with II on both.

DR. HIRSHFELD: Dr. Kandzari?

DR. KANDZARI: I support a declassification to Class II for both. I think that we as a Panel need to avoid a double standard here, that we so unanimously support the cardiac indication, but we have little data for that, and we have more challenges around the pulmonary realm because we simply have data for it. If we had separate studies for myocarditis versus ischemic cardiomyopathy versus acute myocardial infarction, we'd be having today these all same debates in the cardiac domain instead.

I will say that there is one additional advantage that hasn't been raised through the declassification to Class II, and that would be that anybody, like myself, who uses ECMO knows that there is a large opportunity

for iterative improvement in the technology. And I think that the Class II pathway would accelerate and motivate industry and investigators alike to advance those issues that they couldn't do in the more rigid structure of a Class III indication.

DR. HIRSHFELD: Okay.

Dr. Jonas?

DR. JONAS: I support moving both to Class II. I don't believe that it's practical to maintain a circuit as a Class III device. I think that that would simply delay collection of helpful information. And so I suggest moving both to II.

DR. HIRSHFELD: Okay. And Dr. Nathan?

DR. NATHAN: I agree. I think both should be II. I've stated my opinion previously that if you have one as a III and then another as a II, it's a little bit contradictory and confusing. I think there's data to support it as a Class II for pulmonary. And I don't think we should be put off at all by notions that this might be abused in any way. I don't think that's within our mandate to move it to a II. It's good to hear that the FDA has adequate oversights to make sure that it's used appropriately, and I think, clearly, it is effective in the subgroups of patients that we discussed. So both should be a II as far as I'm concerned.

DR. HIRSHFELD: Okay.

MS. WENTZ: Can I get some clarification before we move on to

(e), and that is that the classification for 4c here that everyone recommended Class II or Class III is for the more refined definition of acute hypoxic reversible respiratory failure?

DR. HIRSHFELD: I believe that's correct.

MS. WENTZ: Okay.

DR. NATHAN: Acute hypoxic respiratory. We never know if it's going to be reversible or not --

DR. HIRSHFELD: Yeah.

DR. NATHAN: And if they're going for a lung transplant, it's probably not going to be reversible.

DR. HIRSHFELD: Yeah. Okay.

MS. WENTZ: Okay.

DR. HIRSHFELD: So I think, if I can summarize, and I think we've heard a lot about the -- about question (e) already, as people have explained their rationales. But I think at this point, I can summarize, Dr. Zuckerman, to say that for 4d, there's unanimity that movement to Class II is warranted. For 4c, there are mixed points of view on the Panel. There are people who have advocated for moving to Class II, and there are people who have advocated for not moving to Class II, and there are people are on the plus/minus stage. The preponderance of the opinion appears to be in favor of moving to Class II, but it's by no means overwhelmingly strong.

Now, we did hear a good deal about rationales. And,

Catherine, do you want to pose Question (e) formally, and then we -- I took some notes about what some people said about their rationales? I can share those.

MS. WENTZ: Sure. Okay. Question 4e: In accordance with 860.93, if you recommend a classification other than class III, please discuss the reasons for your recommendation.

DR. HIRSHFELD: Okay. So I could start by -- I think that there were three principal rationales that were aired, and then I'll -- let me just mention them, and then if other Panel members would like to add to those, then please do.

The first was that there was the feeling that movement to Class II would actually provide FDA with an opportunity to write very rigorous special controls that should control a lot of the risk. There were numerous expressions that there's concern that the efficacy data that we have in front of us are weak. And there was concern that the efficacy data were weak both for the cardiopulmonary and for the pulmonary indication. The rationale was expressed that the cardiopulmonary indication has sort have gotten a pass because it's, generally, almost certain imminent death at the time that people begin to approve this, so the need for a control group or the feasibility of a control group is lacking. The story with pulmonary is murkier because there are a number of differences of opinion about whether and when it's appropriate to apply this technology. So there is concern that we

really need to learn more about this.

It was also expressed that there's a need for further innovation in engineering and design, and the opinion was expressed that if it was easier to get to market through a Class II rather than through a Class III and easier to innovate and redesign devices, that being Class II might actually facilitate innovation and the development of newer and more refined designs.

Now, are there other thoughts about that rationale that I did not summarize?

Dr. Lange?

DR. LANGE: The other thought was that going Class II would allow you to either request or mandate that a registry be performed. And in some members' opinions, that would give valuable data, and in other members' opinion, it would "just make me feel good." And either one of those is fine.

DR. HIRSHFELD: Okay. Any other comments from the Panel?

(No response.)

DR. HIRSHFELD: Dr. Zuckerman, is this helpful for you?

DR. ZUCKERMAN: This has been extremely helpful. Thank you, Dr. Hirshfeld and the other Panel members.

DR. HIRSHFELD: Okay. Now, I see we lost our Patient and our Consumer Representative, but we have our Industry Representative. Would you like to make any comments?

MR. THURAMALLA: Yes. I'd like to have a closing comment. I'd like to sincerely appreciate the Panel's understanding of the practical problem for the industry in realizing that this is a system, a combination of several components, and not a single product. That makes a big difference in terms of reporting to the MDR system or other registry system especially for conducting a randomized controlled trial. So thank you for understanding that and discussing it.

Also, classification of the system into Class II for both pulmonary as well as cardiopulmonary would be a big help to the industry because it would reduce the confusion and facilitate better and more optimized products to be brought into the field. With the special controls being put in place, which are already there, I think FDA would have full control; whenever a manufacturer or a company comes with a new indication, then they would be having the full control on that application. So classifying it into a Class II would be a big help.

With that, I thank you all, the Panel members and the FDA.

DR. HIRSHFELD: And I would similarly like to thank the Panel. You've worked very hard. I think we've been presented with a very complex information base and a very difficult decision. And I think everybody has worked very hard and in very good faith and has been very resourceful and creative in sharing a lot of expertise with the Panel. So I'd like to thank everybody for your contributions.

And I'd like to thank the FDA for a tremendous job of assembling a huge knowledgebase and presenting it to us in a very articulate and concise and well-organized fashion.

So with that, I'd like to declare the Panel meeting adjourned.

(Whereupon, at 1:04 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

CIRCULATORY SYSTEM DEVICES PANEL

May 7, 2014

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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